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Improving Management of Hospital-Acquired Infections in The Healthcare Setting Using Antimicrobial Coating

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Abstract

Healthcare-associated infections (HCAIs) have a significant effect on public health globally. However, the occurrence of HCAI is generally considered avoidable. Several new coatings were designed to achieve long-term antimicrobial activity to reduce the risk of implanted device malfunction. These antimicrobial coating strategies are generally believed to have the ability to decrease microbial or even viral quantities on surfaces in clinical environments with significant business investment and scientific research. The additional method of raising biosafety in the hospital setting is recommended when touching surfaces consisting of materials with antimicrobial properties, particularly in the light of the recent outbreak of SARS-CoV-2 in 2020; attention is being drawn even to the viral transmission of the residue on the surface to the human body in a hospital setting, especially in ICU units. Special coatings are believed that to reduce the risk of contamination using antimicrobial surface engineering.

***Keywords*:** healthcare-associated infections; antimicrobial; coating; hospital infections.

Introduction

The term "healthcare-associated infection (HCAI)" has replaced the former ones used to relate to these infections, i.e., infection with "nosocomial" or "hospital infections" [1]. Nosocomial infections or HCAIs can occur within 48 hours of hospital admission, three days of discharge, or 30 days of operation, leading to enhanced patient mortality [2-4]. Hence, on the day a patient is admitted to the ICU, it would be beneficial to estimate the highest risk of HCAI for the patient [5]. In other words, HCAIs are infections acquired by patients during their contact with healthcare [6, 7], and this is a big concern for both healthcare staff and workers (HCW) and patients [2] and forces the cost of healthcare to increase dramatically [8]. Thus, HCAI is regarded as a secondary injury that does not complying with traditional epidemiologic and medical rules [9]. However, HCAIs continue to be one of the leading causes of mortality in several countries due to a spike in antibiotic-resistant bacteria and the hesitation of some HCWs to adopt best-practice contamination controls [2]. Due to these reasons, HCAIs cause a rise in morbidity, death, hospital residence time, and expenses; further study and operational improvements are therefore necessary to ensure the protection and prevention of HCAIs in hospitals [2]. Bacterial, fungal, parasite, or prion contamination may also lead to HCAI; however, bacteria are the most prevalent infection [10]. On the other hand, there has been an increase in the rate of antibiotic-resistant bacteria associated with HCAIs in intensive care units (ICUs) in hospitals [11].

Hence, ICUs are associated with a higher risk of infection than other departments and wards, and patients admitted to this unit are at a higher level of risk of acquiring healthcare-associated infection from different origins [12] as a result of mechanical ventilation, the use of invasive procedures, and their immunocompromised status. Generally, HCAIs can be transmitted by hospital staff members (mostly hands) through direct contact or cross-contamination or from admitted patients in the ICU. Therefore, contaminated stuff such as medical devices (device-associated infections: DAIs), needles, and inanimate surroundings are the sources of these infections [6]. The use of invasive devices in developing countries has increased without preventive steps to monitor infections, leading to higher levels of DAIs than in developed countries [3]. The potential of bacteria to conquer medical surfaces suggests a considerable risk of microbial spread within the patient [13]. In healthcare settings, there are three transmission modes: contact transmission (direct and indirect), droplet transmission, and airborne transmission [3]. Whereas the viral load of coronaviruses on inanimate surfaces was not understood during the pandemic 2020 coronavirus (COVID-19), it seems likely that by surface with disinfecting disinfectants [14] or antimicrobial coating, the highest viral load can be reduced. Also, during the previous pandemic (PDM-09), hospitalized patients infected by influenza virus outbreaks (H1N1) were recorded in some categories, including transplant recipients, pediatric patients, non-hematologic patients, and neonatal intensive care units [15]. On the other hand, respiratory viruses are significant pathogens that cause HCAIs [16]. Hong *et al.* found that 23% of severe nosocomial pneumonia in adults was attributed to respiratory viruses [17]. They are spread indirectly by contact with contaminated surfaces, through direct patients, infected visitors and relatives, and infected HCWs [18]. Infection by setting was described as follows:

> CAI: Infection identified in patients lacking previous contact with HCW within 48 hours of being admitted to the hospital (community-acquired infection) [19].
>
> HAI: Localized or systemic circumstances: a) the outcome of an adverse effect caused by exposure to a contagious agent(s) or related toxin; b) 48 hours or more following hospital admission and not incubating at the time of hospital admission.
>
> HCAI: Infection observed in patients within 48 hours of hospital admission with prior interaction with HCW within one year [20].

The field of medical device coatings using antimicrobials has grown almost 30 times in the past 20 years, with technologies moving from diffusion-dependent only (short-term antimicrobial eluting) to long-term antimicrobial eluting and fundamentally antimicrobial active content. Various antimicrobial method coatings have been produced to reduce infections associated with the implanted devices and prevent the development of biofilms in devices with and without drugs [21]. Recently, microbial biosurfactants have been considered a leading generation of anti-biofilm and anti-adhesive agents to coat medical implants for biocompatibility protection [22]. HCW and a contaminated hospital setting are rapidly involved in distributing and stabilizing multi-resistant organisms (MRO) [23]. These approaches are focused on detecting MRO reservoirs, removing environmental sources, taking measures to interrupt cross-transmission, and proof-based antimicrobial application [23]. Effective administrative aid, and access to current, locally collected information should be enforced in individual responsibility for those measures [23]. However, other cases can be infected. For example, HCAIs from invasive medical devices in the ICU—particularly central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infection (CAUTI)—have been shown to pose the greatest threat to patient safety [24, 25]. In ICU, VAP is the primary cause of morbidity and mortality. It remains a significant concern for hospitalists, following the clinical expertise and substantial advancements in screening tests and administration [26]. Also, implant-associated infection leads to patient pain, financial stress, and mortality, as a typical post-operative complication in orthopedic surgery [27]. Therefore, about 85% of severe sepsis and septic shock patients usually need mechanical ventilator support for 7 to 14 days [28].

Two different types of bacteria exist, planktonic mode of growth (free-floating) and sessile bacteria, which have existed since the first bacteria formed on this planet [30]. Generally, virulence factors contribute to infection after the initial attachment to the coated biomedical device helps form a biofilm [31]. The bacteria's status in either the planktonic or the biofilm type has significant consequences for preventing bacterial infections [32]. However, a new approach to deal with the issue of biofilm formation in medical devices has been thoroughly examined: coating or surface modification to prevent attachment to microorganisms rather than treating mature biofilm [33].

This study aims to test and evaluate the optimal conditions for the antimicrobial properties of the non-coating on medical devices. The efficiency of the coating to resist bacterial or fungi contamination will be assessed against a wide range of bacteria and fungi that can potentially cause wound infections in the hospital. The nanocoating will also be tested for cytotoxicity toward human cell lines *in vitro*. We hypothesize that the metal-based thin film nanocoating may possess antimicrobial properties and provide a cost-effective alternative for preventing hospital-acquired wound infection.

Epidemiology of HCAIs in the world

The US Center for Disease Control and Prevention (CDC) estimates that about 1.7 million admitted patients develop HCAIs per year while being hospitalized for other health conditions and that more than 98,000 of these patients (one out of 17) die from HCAIs [2, 34]. Moreover, HCAI is identified by the US as the fifth most important cause of death in acute care settings [35]. Nearly 1.7 million people suffer from HAI, resulting in 99,000 deaths a year [36]. Although only 6 percent of this country, nearly 2 million HCAIs patients were being avoided in the mid-1970s [37]. Another study by Virginia Commonwealth University in the United States showed that for every 55 (estimated based on the result) with alcohol use disorders undergoing cesarean delivery, one additional patient would develop a nosocomial infection [38]. Cassini *et al*. reported that in the European Union and the European Economic Region, more than 2.5 million new patients are registered as HCAIs patients annually [39], which affects up to 80.000 patients per day at European hospitals [4]. More than 400 thousand infections of antimicrobial-resistant microorganisms associated with healthcare were reported annually in the EU [9]. This is an economic burden, not just for global health. HCAIs also affect critically ill patients, with nearly 0.5 million cases of HCAIs being recorded annually in ICUs alone [40]. However, HCAIs also affect critically ill patients, with nearly 0.5 million cases of HCAIs being recorded in ICUs alone annually [40]. However, antimicrobial activity-resistant microorganisms have reported related deaths in the EU at 33,110 annually [9]. Antimicrobial activity-resistant microorganisms have reported related deaths in the EU at 33,110 annually [9].

Cost analysis of treatment for healthcare-associated infection (nosocomial infection) in the world

The cost of HCAIs is another significant factor in reducing such infections. However, the existence of an HCAI does not automatically reduce the payment revenue for hospitals in healthcare systems that rely on fixed per diem information systems, as additional bedding may be paid to third-party payers [41].

In the USA, the annual cost for HCAIs range from US$28 to US$ 45 billion, but almost 90,000 lives are still lost annually even with this budget: HCAIs are one of the top five assassins in the USA [2]. However, CLABSIs cost prevention from $1.7 billion to $21.4 billion, and in Australia estimated cost of $36.26 million with a death rate of 4-20% [23] and Central venous catheter-related bloodstream infection (CVC-BSI) ranges from $296 to $2.3 billion, recorded cost per contamination about $34,508-$56,000 for catheter-related bloodstream infections (CRBSIs) in annual [42]. The antimicrobial coating (AMC) global market is valued at $1.5 billion, whereas the world demand for AMC is projected to hit $2.9 billion in 2018 [43]. The National Health Service (NHS) in the UK annual expenditure rises for surgical site infections (SSIs) is about £65 million [44], and the extra expense for each person in this country is about €2500 [45].

Biofilm formation on medical devices

Over the past 40 years have recognized microbial

Biofilm formation in healthcare settings is highly troubling because it is understood that it is found in 65 percent of HCAIs and is frequently identified in medical devices and other places, such as water tubing, catheters, and wounds [33]. They are complex colonies that are very resistant microorganisms to antibiotic and antimicrobial therapy, primarily due to their ability to produce extracellular polymeric substances (EPSs) or extracellular matrix (ECM), which play as an inherent barrier for neutralization, detachment, and breakdown [47, 50, 51] and regulate exchanges of ions with the surrounding environment [52]. Typically, a biofilm forms a bacterium that binds to a surface [47]. Biofilms can bind to all structures, including metals, body tissue, plants, implants, and medical devices [53]. EPSs also enclose biofilm cells, create structural stability for the microbial population, and facilitate surface adhesion and cell accumulation. Also, they can conquer medical devices and human tissues, have a well-defined role in the production of microbial pathogenesis only within the last 20 years [46, 54], and cause painful deaths from HCAI infection [55]. Biofilm production involves a bulk inoculum of bacteria that binds the cell to a surface, multiplying the cells, maturation, creating a polymer matrix cellular, and eventually, detachment from the surface, colonization of a new surface, and maturation into a pathogenic biofilm [33, 56]. When cells bind and adhere to surfaces, biofilm formation begins. Factors such as microbial motility, enhanced shear forces, and hydrodynamic and electrostatic interactions between the microorganism and the surface may promote the attachment of microbial cells to biomaterials [53]. In humans, biofilms account for up to 80% of the total number of microbial infections, according to the National Institute of Health [30]. The formation is typically classified into three stages: (i) initial attachment (reversible and irreversible); (ii) maturation of microcolonies; and (iii) dispersion or detachment [30]. This biofilm-mediated phenomenon is antimicrobial-resistant and involved with cell survival, including "persister" cells [46].

The biofilm formation is usually divided into three phases: (i) the first attachment (reversible and irreversible) [52], (ii) the maturation of microcolonies, and (iii) scattering/detachment [30]. Thus, to render the devices safe for patients, it is vital to maintain a high level of sterility, often achieved by different levels of disinfection or sterilization cycles [57]. Despite the strict standards and regulations, SSIs (previously named wound infections) that are hospital-acquired were reported to be among the leading nosocomial causes of morbidity and increasing medical expenses [58], especially following abdominal surgery [59] and joint arthroplasty [60]. Often, it is characterized as microbial surgical contamination within 30 days of surgery or one year after surgery [45]. SSI poses a significant morbidity and mortality risk to healthcare [3], and it is potentially the most treatable HCAI but has attracted the slightest bit of attention [7]. According to the CDC, it is estimated that SSI risk related to abdominal surgery varies between 2 and 8%, based on the type of surgery performed [61]. Also, a double hospital stay may be possible for this risk factor [44]. Recent results indicate that the rates of SSI in warmer climes are high [3]. There was also awareness of the role of biofilms in SSIs; once a biofilm forms on the surface of a suture, its enclosed microbes are resistant to conventional antimicrobials [46]. Hence, the most common bacteria that make a biofilm in SSIs are *Staphylococcus aureus* and *Pseudomonas aeruginosa* [45]. Due to methicillin resistance, MRSA is the worst bacteria [62]. However, for orthopedic studies, SSI is devastating because it is difficult to remove the infections from the bones and joints [63] using antibiotic regimes that are usually successful against planktonic conditions with the same bacteria emerging [46]. It has also become common following hepatobiliary surgery [44]. Seventy-two percent of chronic rhinosinusitis and cultivated microorganisms in biofilms have been found in sinus tissues [47]. Biofilms can also be found in tissue -related infections such as cystic fibrosis (CF), cystic fibrosis with chronic lung infections, chronic obstructive pulmonary disease (COPD), non-cystic fibrosis bronchiectasis, bronchitis, and diffuse panbronchiolitis [47]. Figure 1, which illustrates dental implant infection, catheter contamination, and orthopedic infection, indicates fields vulnerable to a biofilm infection.

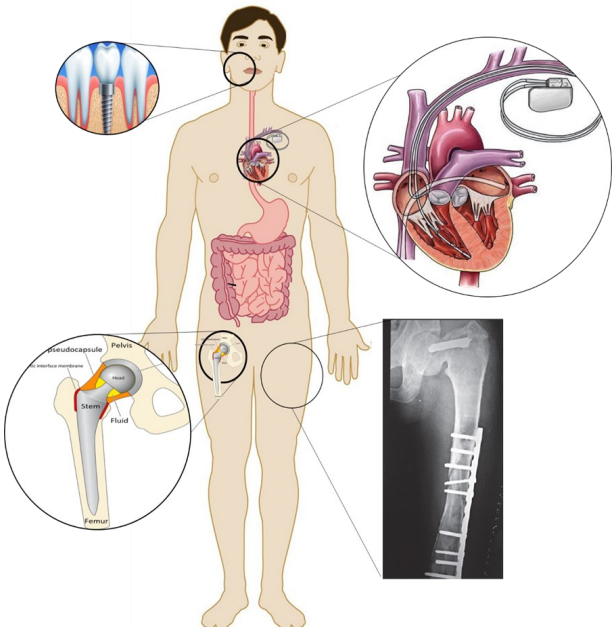

Fig 1. *A typical illustration of assistive devices implanted in a body*

Biofilm affects medical devices and can cause dramatic, recalcitrant infections [51]. Two strategies have been used to control biofilm formation; in medical devices in hospital settings: firstly, to grow biofilm inhibitors depending on a comprehension of the molecular mechanism of biofilm formation; and second, to alter the biomaterials used for the medical device to avoid the formation of biofilm [53]. Also, it can be divided into two main categories: devices that are permanent and those that are temporary. A permanent device is inserted and implanted for an extended period (non-disposable), while a short-period (disposable) temporary device is intended [62]. As a side effect, however, an implant of medical devices also contributes to hard-to-treat pathogens: biofilm-growing microorganisms rapidly become resistant to antimicrobial agents due to colonization on their surface [64]. Although fibrous encapsulation is not dangerous, some devices, like pacemaker power wires, help to prevent unintended movement. Unwanted encapsulation in instruments such as biosensors and orthopedics can, in turn, lead to biosensor malfunction and stop bone growth [62]. Medical equipment, especially for critically ill patients, is responsible for many nosocomial infections [65]. For instance, in some ventilator machines, like ventilator-associated pneumonia (VAP), biofilm formation is a significant issue with mortality due to HCAIs [55]. Hence, the most frequent infectious risk of ICU patients in the latest studies has been demonstrated by VAP [66], in which endotracheal tube surfaces are quickly covered by biofilm, and endotracheal intubation only lasts a few hours to colonize with bacteria [54]. In many studies, Gram-negative bacteria are the most prevalent pathogens that lead to VAP [26], especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [47]. On the other hand, catheters may be used to deliver fluids to a portion of the organ or can be performed to remove disposal fluids [50] and perform hemodynamic observation [67]. However, during medical ventilation (MV), the risk of infection is increased [26], as can be observed for hemodialysis catheters in patients with an enhanced mortality rate [68] due to bacteria that are emitted and may develop pneumonia when aerosolizing biofilms during mechanical ventilation or disturbance during suction by the trachea or hemodialysis catheters [54]. Chelators that interfere with the role of metal ions in forming biofilms are also known as biofilm inhibitors [53]. Table 1 summarizes infection rates for some of the most prevalent implantable medical devices.

In healthcare, contact between medical devices or surgical instruments with patients' tissue or mucus membranes is unavoidable, creating a significant risk factor, *i.e.*, introducing pathogens that may cause serious infections [135]. The medical device surface should be smooth and standardized to maintain biocompatibility, allowing normal development and avoiding invading pathogens [10]. Central venous catheters (CVCs), with infection rates of 3% to 5%, are more vulnerable to device-related contaminations than any other medical device [67]. Drug-resistant bacteria have also emerged as a growing problem in hospitals worldwide, and poor hygiene among staff is often blamed for the spread of such infections [101]. Common pathogens associated with hospital-acquired wound infection are *Staphylococcus aureus*, MRSA, *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis* [2, 59, 136]. Gram-positive bacteria are the leading cause of nosocomial infections where the prevalent pathogen is MRSA is responsible for up to 60 percent of nosocomial infections in ICU, but for central line-associated bloodstream infections (CLABSIs): Gram-negative (39.2%), Gram-positive (33.2%) and *Candida* spp. (27.6%) were the most prevalent causative organisms [2]. There are two polarities in knowledge and understanding of HCAI, with close attention on Gram-positive *Staphylococcus aureus* infections. However, the reality is that Gram-negative bacteria are the more significant threat [4].

Table 2. Typically isolated biofilm microorganisms linked with medical devices

Indwelling Medical device	Microorganisms	References
Central venous catheter (CVC)	*Candida albicans*, coagulase-negative *Staphylococci* (CNS), *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*,	[103, 104]
Catheter	*Candida albicans*, *Mycobacterium avium*	[105, 106]
Endotracheal tubes (ETTs)	*A. baumannii*, *Enterobacter* spp., *Enterobacter faecalis*, *K. pneumoniae*, *Pseudomonas mirabilis*, *P. aeruginosa*, *P. aureus*, *S. aureus, S. epidermidis*	[107-111]
Enteral feeding	*Bacilli*, *C. albicans*, *Candida spp*., *Enterococci*, *Staphylococci*, *Pseudomonas*	[112, 113]
Intravenous and peritoneal catheters	*C. albicans*, *Chryseobacterium meningosepticum*, *Klebsiella ornithinolytica*, *K. pneumoniae*, *P. aeruginosa*, *Staphylococcus lugdunensis*, CNS, *S. aureus*, *S. epidermidis*	[111,114-117]
Prosthetic joint (artificial hip prosthesis)	*Bacterioides* spp., CNS, *enterococci*, *E. coli*, E. *faecalis*, *E. faecium*, *S. aureus*, *S. epidermidis*, MRSA, *Proteus mirabilis*, *P. aeruginosa*, Viridans *Streptococcus*	[104,118-122]
Prosthetic heart valve	CNS, *enterococci*, Viridans *Streptococcus, S. aureus*	[104]
Pacemakers	*S. aureus*	[123, 124]
Urinary catheter (CAUTI)	*Acinetobacter lwoffi*, *A. baumaunnii*, *C. albicans*, *E. faecalis*, *Escherichia coli*, *Enterococci*, *K. pneumoniae*, *K. ornithinolytica*, *Proteus mirabilis*, *P. aeruginosa*, CNS, *S. aureus*, *S. epidermidis*	[10, 104, 111, 121, 125-131]
VAP	*Candida*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. epidermidis*	[111, [121,132]
Voice prosthesis	*C. albicans, Candida tropicalis*, *Rothia dentocariosa*	[133, 134]

The most prevalent fungus of the genus *Candida* spp. is *Candida albicans*. In general, 10% of all CLABSI infections related to catheters are septicemias caused by *Candida* species [33]. *S. aureus* and *S. epidermidis* are primarily cardiovascular devices that lead to biofilm formatin. An estimated 40-50% of prosthetic heart valve contaminations and 50-70% of catheter infections are caused by these two bacteria [53]. All these bacteria are responsible for increased hospital death rates and significantly affect on patient conditions [67]. *Acinetobacter* spp. has the potential for colonization and creating biofilms on medical devices such as heart valves, implants, catheters, artificial joints, *etc*. [137]. Also, this pathogen has been identified as the most significant nosocomial infection implicated in several HCAI infections, including urinary tract infection (UTI), bacteremia, secondary meningitis, and soft-tissue infections [53]. The new host may attach to the microorganisms by ingestion, breaks in the skin barrier, inhalation, *etc*. [50].

Implants and prosthetic medical devices can become these new hosts because the infection may have life-threatening bacterial contamination [30]. Numerous factors, such as enhanced cell movement, shear forces, and electrostatic interactions between microorganisms and surfaces, may help promote this attachment [33]. Bennet *et al*. found that the existence of an invasive device is the most significant risk factor for HCAI development [25].

Infection can happen using an indwelling medical device such as catheters, ventilators, endoscopes, and shunts or by contacting contaminated surfaces or contamination with airborne fungal spores during performing surgery [138]. On the other hand, several medical devices, such as hernia meshes, orthopedic implants, catheters, and vascular grafts, develop serious infections to a higher level of severity [21]. Catheter, vascular graft, orthopedic, and hernia mesh coatings are among the widespread applications of affinity-based metal device coatings (Figure 2).The research aimed at improving to the design and antibiofilm properties of these devices is complex and restless, given the aggressive nature of biologic-related infections that have formed on medical devices, particularly those that come in contact with high tissue surfaces [48].

There are specific ways to prevent the formation of biofilms without affecting device biocompatibility, such as the creation of new materials, modification of surface composition, and modification of chemical surface [139]. New biomaterials with antibiofilm characteristics can be produced. However, they will require substantial expenses, as many additional properties, including mechanical properties, physicochemical stability, *etc*., must be considered during their development [139].

There have been numerous methods to achieve biofilm inhibition; however, the complex structures of specific microbial communities restrict their effectiveness [48]. The most typical type of HCAIs is urinary tract infections (UTIs) which are commonly associated with catheters (31%), followed by SSIs (17%), primary bloodstream infections (BSIs) which are usually related to the application of an intravascular device (14%) and the last one pneumonia (generally associated with ventilator machines) (13%) [58]. One study showed that 73.33% of orthopedic surgery cases were culture-positive, with a total of 35 bacterial strains insulated,

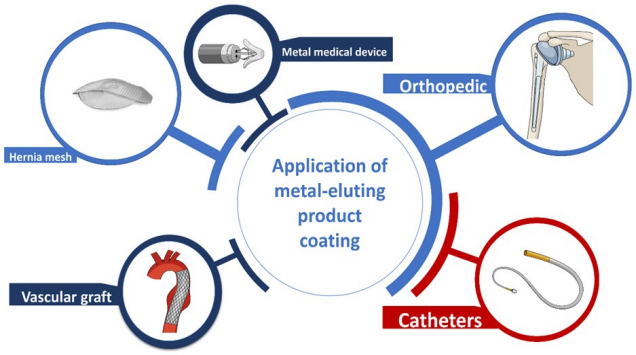

Fig 2. Application of metal-eluting product coating on some medical devices

with 65.72% Gram-positive and 34.28% Gram-negative [140]. Nevertheless, ICU stays were more prolonged in patients who suffered from SSI [59]. A study by Bennet *et al*. showed that device-associated infection rates per 1,000 days were increased endotracheal tube followed by urinary tract and central venous catheter [25]. Medication is typically treated with a wide-spectrum antibiotic such as vancomycin. However, vancomycin-resistant enterococci and cases from vancomycin-resistant *S. aureus* are identified [141]. According to Vincent *et al*., *S. aureus* (30.1%); [60% resistant to methicillin] was the second most frequently reported microorganisms followed by Enterobacteriaceae (especially *A. baumannii*) at 34.4% [142].

The role of Quorum sensing in biofilm formation

A closely controlled communication mechanism called quorum sensing (QS) in several Gram-negative and Gram-positive bacteria was discovered that occurs between these bacteria [32] which is an essential cellular interaction mechanism [53], physiological proceedings such as pathogenicity, programmed cell death, creation of bacteriocin, genetic abilities, symbiosis, development of spore, and the formation of biofilm [143]. Signal activation from QS may result in pathogens' antimicrobial resistance, which makes the disease hard to cure [144]. This quorum sensing can contribute towards organizing the colony's overall growth and coordinating the formation of biofilms, likely linked to the paracrine hormonal system of interaction in eukaryotic organisms [32]. Quorum-sensing molecules produce gradation-based signals that help biofilm differentiation and regulate and change the expression of many genes [52]. Some proteins, such as SasG in *S. aureus* and Aap in *S. epidermidis* tend to play a role in intercellular adhesion [32]. On the other hand, the *S. epidermidis* QS regulator also seems to be participating in biofilm detachment, boosting biofilm growth with an isogenic *Agr* mutant [145]. Any process interrupting QS signals can be used to avoid or minimize virulence in the target setting, to alleviate the viability of the bacteria [47]. Quorum-sensing inhibitors (QSIs) can prevent the formation of biofilms [146].

QSIs methods are as follows: (i) disorder of signal molecules biosynthesis, (ii) use of QS antagonists such as application of some extracts from algae, plants as well as other chemical substances, (iii) inactivation of a compound of QS signals, and (iv) signal molecules biodegradation [47]. During signaling, the bacteria inside the biofilm feel the concentration and amounts of microorganisms in a biofilm. Not every biofilm generates the same chemical signals. For instance, Gram-negative bacteria release molecules called acyl-homoserine lactones, while Gram-positive bacteria release peptide substances [50]. In contrast, every microbial species seems to have its collection of QS systems [56]. Three critical approaches to monitoring biofilm formation or targeted specific phases of biofilm production have been recognized. First, bacteria's initial binding to biofilm-forming surfaces would be hindered, thus reducing the risk of biofilm growth.

The second method is planned to interrupt biofilm during the period of development. The third is the signal interference method that QS coordinates; biofilm formation or maturation in microorganisms interfere with the bacterial communications system, or QS networks [53].

Antimicrobial coating as emerging resistant microbial inducers

In the war against HCAIs, AMCs are a fairly new technical alternative [4]. The expanded use of AMCs has raised fears about the existence of resistant pathogens in recent years [43]. To improve current hygiene practices and to help counter the growing risk of antimicrobial resistance, antimicrobial touches have been added to the healthcare setting [147]. This resistance development has a major effect on healthcare settings because of the contamination of medical devices and the subsequent spread of these device-related infections [33]. According to Ahonen and colleagues, the techniques for minimizing and monitoring the release of active agents from AMCs can be classified into four major groups: (i) reactive methods for regulating antimicrobial release by changing the carrier matrix to the correct size like monitoring the pores through that the antibacterial is mounted; (ii) passive antimicrobial release control approaches with the addition a thin polymer layer, which has been shown as key factors for discharge kinetics, thickness, hydrophobicity or the level crosslinking of the polymer layer; (iii) antimicrobial stimulating substances that include shrinking, swelling, or bending polymers; and (vi) active regulation of antimicrobial release by the pathogen itself; for example, pH-responsive polymers that alter their combination during acidic conditions, following the discharge of different biochemical substrates by bacteria or compounds that immobilized by pH-sensitive amide bonds on the surface of nanoparticles [43].

The levels of antimicrobial resistance (AMR) remain poorly represented in many countries after the introduction of the Global Antimicrobial Resistance Surveillance Program (GLASS) [148], and AMR represents a global health issue [3]. Plasmids, bacterial chromosomes, and, transposons can carry AMR genes [36]. To understand how AMCs risk influences the development and spread of AMRs in healthcare settings, two facts are leading; cross-resistance and co-resistance [147].

Decolonization and decontamination of biofilm on medical devices using antimicrobial coating

New methods have been discovered according to the problem of AMR eradicating biofilms. Bactericidal applications have been emphasized for performing in healthcare facilities. the possibilities for these coatings have been established based on literature and studies, among others, gold ions, silver, titanium, or organosilane used under laboratory requirements [4]. In this example, surface alteration for medical devices is the most common technique [33]. Currently, most AMCs are depend on the release from the surface of the active chemical. The typical patterns of the discharge of nano-enabled coatings from active agents follow the kinetics of the first or second order, namely an initial rapid release proceeded by a reducing tail typically varying from hours to a few days [43]. The focus on high-precision processing has risen steadily, mainly in the next generation's semiconductors, electronic sector, and aerospace. This classification of high-precision manufacture includes creating thin films, a coating layer a few micrometers thick. These films vary significantly from those bulk materials or the substrate on which the film is mounted.

Applying cyclodextrin (CD) polymers in medical device coating is exclusively advantageous since they have been scientifically proven to maximize antibiotic loading in devices by ten times and have shown efficacy for almost eight months in *in-vitro* conditions and regulated transmission *in vivo* for nearly one month [21]. The use of silver nanoparticles for medical purposes is a relatively recent and generally accepted technique with speedy manufacturing capabilities and minimal effects on human health and environmental sustainability [146]. An efficient application for introducing antibiotic resistance bacteria is silver nanoparticles (AgNPs). As a membrane-mimetic template, Green AgNP's (G-AgNP) can interfere with phospholipid bilayers [149]. These nanoparticles cause to produce oxidative stress on some bacteria, such as *E. coli*, *P. aeruginosa*, *S. aureus*, on their lipids, proteins, DNA, and death of bacteria [150]. Also, Pallavicini *et al*. found that after 15 days, when the surfaces are exposed to water, approximately 15% of silver released Ag+ ions. The release of these ions contributes to successful antimicrobial activity against harmful bacteria such as *E. coli* and *S. aureus* [151]. A study by Francolini *et al*. showed the anti -biofilm efficacy of silver ion-combined polyurethanes, which are polymers specifically ideal for creating various of medical devices, including vascular grafts, cardiovascular implants, artificial heart and assist devices and catheters [152]. In comparison, using silver nanoparticles impregnated in central venous catheters did not affect the colonization of catheters, CLABSI, or death rate in severe patients [153]. On the other hand, based on natural products, Diez-Pascual found that linseed oil (vegetable oil contains antimicrobial activity) reinforced with titanium dioxide can be used as an antimicrobial coating against Gram-negative *E. coli* and Gram-positive *S. aureus* bacteria. Her study showed that these nanocomposite coatings may be used in common areas with a high risk of contamination like hospitals [154].

The latest clinical research has demonstrated that a few human pathogen bacteria die when they make contact at ambient temperature with dry copper and copper alloy surfaces [155]. Copper alloys (Cu-ETP) showed antibacterial activity against *A. baumannii* strains. Their findings have shown effective activity such as bacteriostatic and bactericidal, as opposed to stainless steel [156]. Von Dessauer *et al*. has also reported a positive influence of AMC on reducing HAI, which suggested that for both copper and non-copper to exposed patients, HAI levels were 10.6 against 13.0 per 1,000 patient days, respectively, although not substantially different significantly [157]. Rozanska *et al*. found that copper alloy possesses antimicrobial activity against *S. aureus* and *E. coli*; however, *S. aureus* showed more resistance [158]. The efficacy of copper alloys in antimicrobials is typically proportionate to the copper quality of a given alloy [158]. Salgado *et al*. observed a dramatic decrease in the HAI incidence and MRSA or vancomycin-resistant Enterococcus formation in the intervention group of the research compared to the control group with the minimal addition of 6 copper materials [29]. Some findings also indicate that applying copper to solid touch surfaces of patient rooms or copper, including linen, can reduce HCAI versus non-copper sample surfaces [29, 43]. This led to the development of vast interest in research involving highly efficient and low-cost antibacterial surface treatments that may protect from the breeding and spreading of harmful microorganisms on medical devices [151, 159]. Among the technologies used, nano-coatings are already finding application in the healthcare industry to enable antibacterial surfaces for medical catheters, added to paints and lacquers used to coat operating tables, doorknobs, and door handles in hospitals, and as ultra-hard porous coatings for surgical and orthopedic implants like screws, plates or joint implants [160].

It is necessary to protect these materials and surfaces with a high level of hygiene using antimicrobial agents since it will provide protection against bacteria and fungi and significantly reduce in health costs. The use of nano-silver coatings technology on medical devices has been reported due to its potent antimicrobial efficacy against a broad spectrum of bacteria, fungi, and viruses [161-164].

However, caution is necessary. The development of nano-coatings using innovative active compounds (for example, nano-silver), many of which are impacted by specific methods of end-user cleaning processes, will result in the release of bioactive compounds and promote possible exposure as low amounts of these to human and environment [4].

Although the mechanism of inhibition is not fully known, silver ions were reported to interact with bacterial proteins and enzymes to damage the cellular wall and bacterial membrane as well as lead to a condensed form of DNA molecules to render the bacteria to lose their ability to replicate [27, 165, 166].

Apart from silver, copper has also been reported to possess antimicrobial activity and is widely used for surfaces in healthcare settings [8], especially on *Acinetobacter* species [156]. Raad *et al*. examined *in vitro* the efficacy of antimicrobial gardine and gendine-coated endotracheal tubes (ETTs) against silver-coated ETTs. They eventually demonstrated that some bacteria, such as *Pseudomonas aeruginosa*, MRSA, *Klebsiella pneumonia,* and *Candida albicans* biofilm growth may be prevented totally with gardine and gendine-coated ETTs for up to 14 days, compared with the silver-coated ETTs that still showed growth of increasing to 10^7 CFU/cm [167].

In recent years, various studies assessing the use of copper in hospital-based environments as a technique for decreasing the microbial burden and preventing HCAIs have raised [8]. Many findings demonstrated that the copper touch surfaces examined in the hospital and kindergarten contain lower total bacteria like *S. aureus* than non-copper touch surfaces [168]. However, there have been few published studies of copper's clinical efficacy, and these surfaces are also expensive. However, Souli *et al*. reported the sensitivity of the strain from *Acinetobacter* sp. to copper and brass CuZn [169]. Thus, it is of utmost importance that the medical devices and environments are maintained at a very high level of sterility, often achieved by sterilization methods set on high specific standards to render the devices used to be safe for patients. There are different levels of disinfection or sterilization cycles, depending on the instrument's intended use. Items such as surgical instruments, which have direct contact with tissues, are considered critical and require to be sterilized. Semi-critical items include endoscopes, which only contact mucous membranes and require high-level disinfection. Noncritical objects, like stethoscopes must be disinfected at a low level.

Antimicrobial coating as emerging resistant microbial inducers

Because of its decreased antimicrobial resistance, removing a biofilm from the medical system is complicated [33]. There are different methods for the deposition of thin films, commonly called processes for vapor deposition. Vapor deposition processes can be categorized as chemical vapor deposition (CVD) or physical vapor deposition (PVD), depending on the source of the vapor to be deposited. The PVD procedure is more commonly used to create thin films among the two [170]. Vapors are produced, either alone or in combination, using resistive heating, atomic sputtering, ion placement, magnetron sputtering, or lasers [171]. Initially used to coat polyurethane catheters and silicone shunting, hydrophilic polymers such as hyaluronic acid and poly-N-vinylpyrrolidone have been shown to minimize adherence of the *S. epidermidis* successfully [172].

Due to their ease of composition control or system operation, sputtering processes are commonly used in PVD deposition [173]. *Sputtering* is a process that removes atoms from the surface of a substance because of high-energy ions in PVD deposition [173], and it removes atoms from the surface of a substance because of high-energy ions. The atoms and molecules are expelled from a goal material by high-energy electron bombardment during the sputtering PVD phase so that atoms or molecules can jam on a substrate as a thin film. The target material is a plate-shaped solid metal element, alloy, or ceramic compound. The quality of the sputtering depletion method is also an issue associated with solid disc-based targets. The main issue is the complexity of gaining in-plane uniformity in the deposition frequency and forming a stable deposition of films [174-176]. Some studies have suggested penetration techniques using powdery or granular targets to resolve the limitation. Therefore, here, we propose to investigate and optimize the antimicrobial properties of the thin-film metal-based coating developed by our collaborators from the engineering faculty.

Conclusion

Each healthcare provider is responsible for adopting guidelines for preventing infections associated with healthcare, but not all infections can be avoided. Since healthcare expenses are substantially higher than previously predicted, and massive investment in infrastructure and staff training is targeted to achieve a higher quality of patient throughput than previously anticipated, there still is a pathway for slowing or preventing antimicrobial resistance using new methods and innovations.

Disclosure statement

The authors declare that they have no conflict of interest

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