Bio-Design and Manufacturing (2026) 9:292–317
https://doi.org/10.1631/bdm.2500199

REVIEW

Strategies for combating central venous catheter-related bacterial infections

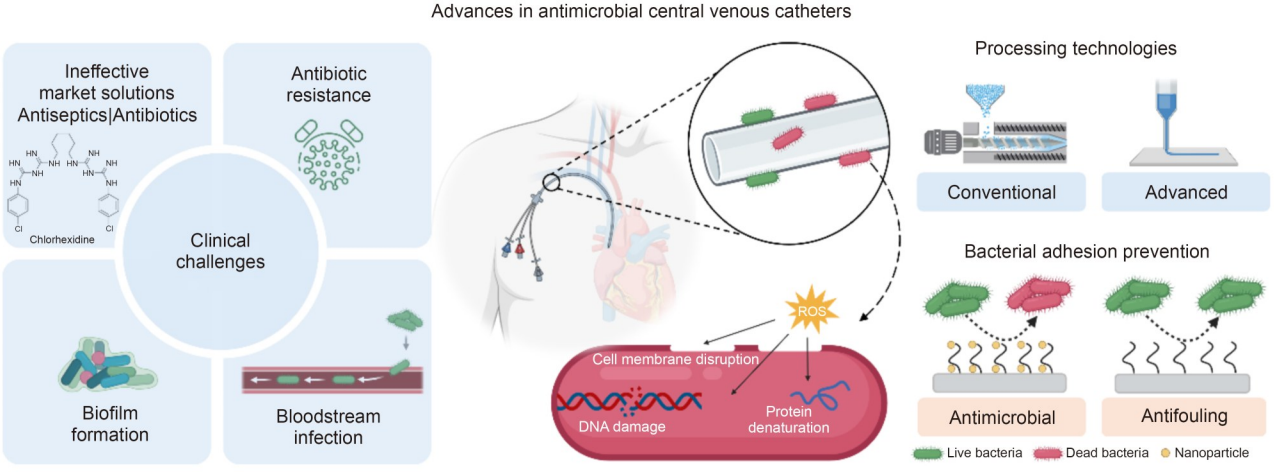
Tatiana Padrão[1,2,3,4] · Fernando J. Monteiro[1,2,4] · Juliana R. Dias[3] · Susana R. Sousa[1,2,5]

Received: 22 April 2025 / Accepted: 28 August 2025

Abstract

Central venous catheters (CVCs), which play a vital role in medical care and are widely utilized in intensive care units, are highly susceptible to microbial colonization, thus leading to serious catheter-related bloodstream infections and greatly increasing morbidity, mortality, and healthcare costs, accounting for 12%–25% of annual mortality in the USA. The corresponding preventive measures include the use of antibiotic and antiseptic coatings, impregnated catheters, and maximally sterile barrier techniques, but they are often ineffective, particularly against biofilm formation and antibiotic-resistant bacteria. This review focuses on strategies for fabricating antimicrobial CVCs, e.g., the use of antifouling materials, antimicrobial nanoparticles (NPs), and surface functionalization, covering both commercially available solutions and those investigated. Additionally, we explore the materials and processing technologies used to fabricate antimicrobial CVCs, emphasizing their advantages and challenges in industrial and clinical applications. Finally, we discuss the potential of inorganic NPs and the origin of their antimicrobial activity, providing insights for future advances in infection prevention that will help improve the patients' life quality.

Graphical abstract



Keywords Additive manufacturing · Antimicrobial strategies · Catheter production · Catheter-related infections · Central venous catheters

Fernando J. Monteiro, Juliana R. Dias, and Susana R. Sousa have contributed equally to this work.

✉ Tatiana Padrão
tatiana.padrao@i3s.up.pt

✉ Susana R. Sousa
ssousa@ineb.up.pt

1 i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-135 Porto, Portugal

2 INEB – Instituto de Engenharia Biomédica, Universidade do Porto, 4200-135 Porto, Portugal

3 CDRSP – Centro para o Desenvolvimento Rápido e Sustentado de Produto, Instituto Politécnico de Leiria, 2430-028 Marinha Grande, Portugal

4 FEUP – Faculdade de Engenharia, Universidade do Porto, 4200-465 Porto, Portugal

5 ISEP – Instituto Superior de Engenharia do Porto, Instituto Politécnico do Porto, 4249-015 Porto, Portugal

1 Introduction

Central venous catheters (CVCs) are important medical devices frequently used in clinical practice, particularly in critically ill patients, such as those in intensive care units (ICUs), and undergoing chemotherapy [1–3]. CVC selection depends on factors such as intended use, insertion method, location, and duration, with typical CVC materials including polyurethane (PU) and less frequently silicone or polytetrafluoroethylene (PTFE) [4]. The inert CVC materials are prone to microbial colonization, which often leads to biofilm formation and catheter-related bloodstream infections (CRBSIs) [5, 6]. CRBSIs have a frequent incidence and induce serious complications, with catheter colonization rates ranging from 6% to 20%, depending on patient risk and setting. This colonization progresses to bloodstream infections in 10%–20% of the cases, although rates as high as 59% are observed in high-risk or ICU settings [7–9]. In the USA, CRBSIs cause 250 000 to 400 000 cases of nosocomial bacteremia each year, with approximately 80 000 of these cases corresponding to ICU infections [10, 11]. The resulting financial burden ranges between $296 million and $2.3 billion [10, 12]. CVC-related infections represent a notable healthcare concern, leading to high morbidity rates and extended hospital stays, with the corresponding mortality rate ranging from 12% to 25% [8, 13–15].

CRBSIs primarily occur through the migration of skin flora along the catheter surface to the tip, direct contamination from hands or fluids, hematogenous spread from other infection sites, or (less commonly) from contaminated infusates [3, 11]. Conventional treatment often requires catheter removal or replacement along with antibiotic administration, but it is usually ineffective against biofilm formation or antibiotic-resistant bacteria [16]. Therefore, novel strategies and materials for preventing microbial colonization are urgently needed.

This review provides an overview of CVCs, focusing on their types, clinical use conditions, materials, and fabrication technologies. Moreover, we discuss the risks of infection associated with CVC use and examine the structural characteristics of bacterial colonization and biofilm formation. Current prevention strategies (implemented in clinical practice and in early development stages) are discussed, particularly with regard to antimicrobial and antifouling materials. Additionally, we evaluate the role of commercial antimicrobial CVCs through a benchmarking analysis of available products and explore the widely accepted antimicrobial mechanisms produced by various metal nanoparticles (NPs), subsequently focusing on conventional and advanced strategies for fabricating bioactive CVCs.

2 Central venous catheters

Intravascular access devices (catheters) are increasingly used for the administration of fluids, medications, blood products, and nutrients, as well as for hemodynamic function monitoring and hemodialysis. Catheters are classified according to factors such as the type of accessed blood vessel (e.g., peripheral, central venous, or arterial), duration of use, insertion site, and specific features (e.g., presence of a cuff and impregnation with agents such as heparin, antibiotics, or antiseptics) [11, 17].

A CVC, or central line, is a long, soft, flexible tube inserted into the proximal third of the superior vena cava, the inferior vena cava, or the right atrium. CVCs are longer and wider than peripheral venous catheters and are commonly inserted into the subclavian, jugular, and femoral veins [18]. Such catheters offer several advantages, including the ability to administer fluids directly into a large vein and the ability to remain in the body for an extended period. Given that CVCs can remain in place for weeks or months, they are more likely to cause serious infections than other catheters [11].

CVCs are used in the treatment of several clinical conditions, such as critical care, continuous hemodynamic monitoring, difficult peripheral venous access, renal replacement therapy, intravenous administration of high-osmolality solutions, blood transfusions, parenteral nutrition, and prolonged intravenous treatments (e.g., antimicrobial therapy and chemotherapy) [19, 20].

CVCs can be categorized according to the insertion site (subclavian, femoral, jugular, or peripherally inserted central catheter), dwell time (short, mid, or long term), clinical use (acute or chronic), insertion route (tunneled, nontunneled, or implanted), and structural features, such as length and number of lumens (single, double, or triple). Table 1 provides a comparative summary of commonly used CVCs.

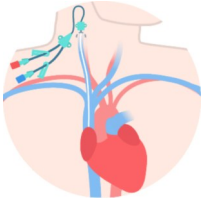
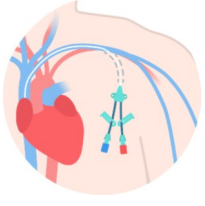
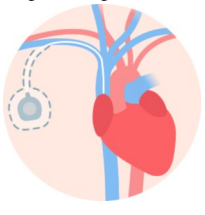
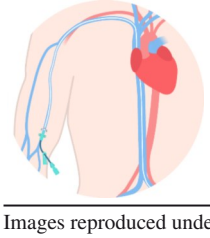
2.1 Market overview

According to the iData Research Report, the global CVC market was valued at approximately $763 million in 2020, with more than 27 million CVC placements performed each year. This market is projected to grow at a compound annual growth rate of 5.5% and reach a cost of $860 million by 2026 [22].

The acute CVC segment, designed for short-term access (<30 d), represents the largest share of the market, particularly in the USA. This segment is a key growth driver, supported by the consistent demand and increased adoption of advanced CVC kits [22].

In Europe, the acute CVC segment is predominant. The slight growth anticipated in the coming years is expected to be primarily driven by the increased use of antimicrobial catheters in high-risk patients. These catheters are priced

Table 1 Comparison of CVC types based on principal characteristics [11, 19–21]

CVC type	Insertion site	Intended life span	Clinical conditions	Insertion skill required	Infection risk	Additional features	Key advantages	Examples
Nontunneled catheters 	Inserted percutaneously into a central (e.g., subclavian, internal jugular, or femoral) vein	Short-term (days to weeks)	Acute care, ambulatory care, emergency situations, and ICUs	Basic skills and no surgical requirements	Higher than for other types	Single or multiple lumens	Rapid placement, ideal suitability for urgent or temporary access, cost-effectiveness for short-term use	Not available (NA)
Tunneled catheters 	A subcutaneous tunnel is created, with the catheter tip positioned in the superior vena cava	Long-term (>30 d)	Multiple accesses over extended periods, e.g., chemotherapy, home nutrition, long-term antibiotics, and hemodialysis	Surgical insertion required	Lower than for nontunneled CVCs	Cuffed or uncuffed options, with the Dacron cuff promoting stabilization by encouraging tissue ingrowth around the tunneled section of the catheter	Suitability for long-term therapies, stable placement, reduced risk of infection	Broviac, Hickman, Groshong, Quinton catheter
Implanted ports 	A subcutaneous reservoir is accessed using a needle, with the catheter tip positioned in the subclavian or jugular vein	Long-term	Long-term access with low infection risk and better cosmetic outcomes	Surgical implantation required	Lowest	Needle access through an intact self-sealing skin septum	Excellent external appearance, minimal daily care, very low infection risk	Port-a-Cath, BardPort, PowerPort, Mediport, Infuse-a-Port
Peripherally inserted central catheters 	Peripheral (usually basilic, cephalic, or brachial) vein into the superior vena cava	Mid-term	Situations requiring mid-term intravenous access	No special surgical skills needed	Moderate but lower than that for nontunneled CVCs	NA	Insertion in a standard clinical setting, flexible duration of use	NA

Images reproduced under license from https://www.istockphoto.com/ (art4stock)

higher than conventional ones, and their widespread adoption is expected to boost market growth in Europe [22].

According to the Pharma and Healthcare-Central Venous Catheters Market Analysis published by Reports and Data, nontunneled catheters were most favored in the global CVC market in 2019 and are projected to retain this position over the coming years [23]. Market segmentation by design includes single-, double-, and multi-lumen catheters, with multi-lumen ones gaining popularity because of their advantage in continuous or intermittent drug infusions. PU catheters generate the highest revenue, followed by silicone and polycarbonate ones [23].

Teleflex, Becton Dickinson, and Cook Medical, which collectively held a leading share of the global CVC market in 2020, are key industrial players [22]. The key factors driving CVC market growth include the rising incidence of chronic conditions such as cancer, kidney failure, and cardiovascular diseases; aging population; increased demand for minimally invasive surgeries; and technological advancements in hospital and home-based healthcare systems [24].

Beyond the market size, the economic burden of CRBSIs further underscores the urgency for innovation. In the USA, the incidence of CRBSIs in general hospital settings is associated with a mortality rate of approximately 12% and costs of $69 000–$71 000 per episode [25]. Studies focusing on ICUs report even higher costs of up to $129 000 per index hospitalization, which is primarily driven by prolonged duration of stay (7–17 d) and intensive care requirements, with

each additional hospital day costing $15 000–$20 000 [26]. In Europe, the cost per CRBSI episode ranges from €13 500 to €30 000 [25]. CRBSIs represent a considerable annual economic burden at a national level, with estimates in the USA ranging from $296 million to $2.3 billion and reflecting critically ill ICU patients and wider hospital populations [11, 12]. These figures highlight the urgency and market relevance of combating CVC-associated infections (e.g., via the adoption of antimicrobial catheters and improving infection prevention protocols), which can notably improve patient outcomes while reducing healthcare costs.

2.2 Central venous catheter-related infections

Vascular access devices of all types pose infection risks and often provide a route by which microorganisms enter the bloodstream and cause a life-threatening condition, CRBSI, which is the leading cause of nosocomial infections [10], substantially contributing to morbidity, mortality, and long-term hospitalizations and increasing resource usage and healthcare costs for pediatric and adult patients [27].

Infection risk varies by catheter type, design, and dwell time. Peripheral venous catheters, typically inserted in the arm or hand for short durations (⩽72 h), pose relatively low risks, whereas CVCs are more frequently associated with severe infections [27]. Tunneled, cuffed, or implantable devices generally show lower infection rates than nontunneled CVCs, with totally implantable ports being the safest for use [20, 27].

CVC-related infections are often caused by skin flora [8]. Colonization may occur within 24 h of insertion via extra- and intra-luminal colonization. Extraluminal colonization begins at the skin insertion site and spreads along the catheter surface. This route is most commonly responsible for infections associated with the use of short-term catheters, particularly nontunneled CVCs used in ICUs, and is often linked to contamination during insertion or implantation [28, 29]. In contrast, intraluminal colonization originates from the catheter hub or occasionally from contaminated infusates and is more relevant for long-term catheters that are subjected to frequent handling and manipulation, such as tunneled catheters used in chemotherapy or parenteral nutrition. Occasionally, hematogenous spread from a distant infection site may also occur (Fig. 1) [8, 27].

Initially, extraluminal contamination is predominant, with intraluminal colonization subsequently becoming more prevalent [28]. Therefore, preventive strategies must focus on the insertion technique and catheter maintenance.

CVC-related infections include local (exit site, tunnel, and pocket) infections and CRBSIs. Local infections typically manifest through inflammation or purulence, whereas CRBSIs often manifest through fever, potentially progressing to sepsis or septic shock without another identifiable source. CRBSI is clinically defined as bacteremia or fungemia in a patient with a catheter presumed to be the infection

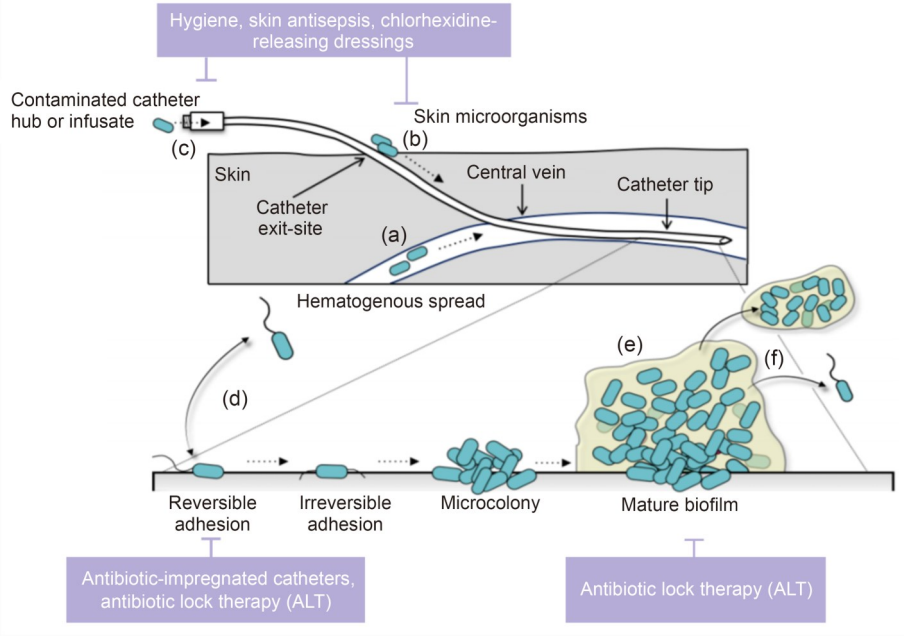


Fig. 1 Origins of CVC-related infection: (a) hematogenous spread; (b) external catheter surface; (c) internal catheter surface. Biofilm development stages with corresponding prevention measures: (d) initial and reversible attachment; (e) merging of microcolonies into a mature biofilm; (f) spreading of cells into the surrounding environment. Reproduced from [30], with permission from Springer-Verlag Berlin Heidelberg and ESICM

source [10]. Bacteremia is the most concerning and clinically important condition associated with CVC-related infections because of its potential to progress to sepsis [27], with additional complications including endocarditis, thrombosis, stroke, and myocardial infarction [12].

CRBSI is typically caused by coagulase-negative Staphylococci, especially *Staphylococcus epidermidis* (*S. epidermidis*, 40%–50% of all cases) and *Staphylococcus aureus* (*S. aureus*, 10%–20%). Other bacteria (e.g., *Pseudomonas aeruginosa* (*P. aeruginosa*), *Stenotrophomonas* sp., and *Acinetobacter baumannii* (*A. baumannii*)) and fungi (e.g., *Candida* sp.) are less frequent in incidence (⩽10%) but clinically relevant [7, 27, 31].

Although *S. epidermidis* has low intrinsic virulence, its ability to form biofilms on medical devices makes it a major pathogen in immunocompromised or critically ill patients [32]. Once bacteria adhere to a catheter, they colonize its internal and external surfaces and form biofilms thereon [33], with *S. epidermidis*, *S. aureus*, *P. aeruginosa*, and *Klebsiella pneumoniae* (*K. pneumoniae*) being the predominant biofilm producers [29].

2.2.1 Bacterial colonization and biofilm formation

Bacteria are unicellular microorganisms comprising a cell membrane, cytoplasm, and a cell wall providing structural integrity and influencing susceptibility to antimicrobial agents [34]. Based on their structural composition, bacteria are classified as Gram-positive, i.e., those with a thick (30–100 nm) peptidoglycan layer (e.g., *S. aureus* and *S. epidermidis*) or Gram-negative, i.e., those with a thin (5–10 nm) peptidoglycan layer and lipopolysaccharide-rich outer membrane (1–3 μm; e.g., *Escherichia coli* and *P. aeruginosa*) [35, 36].

Although most bacteria are harmless, some cause conditions such as pneumonia, tuberculosis, respiratory and urinary tract infections, and bloodstream infections [37]. Bacteria typically exist in planktonic (free-floating) or sessile (surface-attached or contained within biofilm) forms.

Surface adhesion depends on bacterial factors (Curli fibers, pili, flagella, and adhesins) and surface properties (chemistry, charge, wettability, roughness, and surface area). Curli fibers and pili aid initial attachment, while flagella facilitate movement and adherence under fluid flow (Fig. 2a) [38]. Surface characteristics also affect bacterial adhesion (Fig. 2b) [39]. Most bacterial surfaces have a net negative charge due to the ionized phosphoryl and carboxylate groups of the macromolecules on the outside cell envelope, which leads to repulsion from negatively charged surfaces and hinders adhesion [40, 41]. Hydrophilic surfaces are generally more resistant to bacterial adherence than hydrophobic ones because of the presence of hydration layers

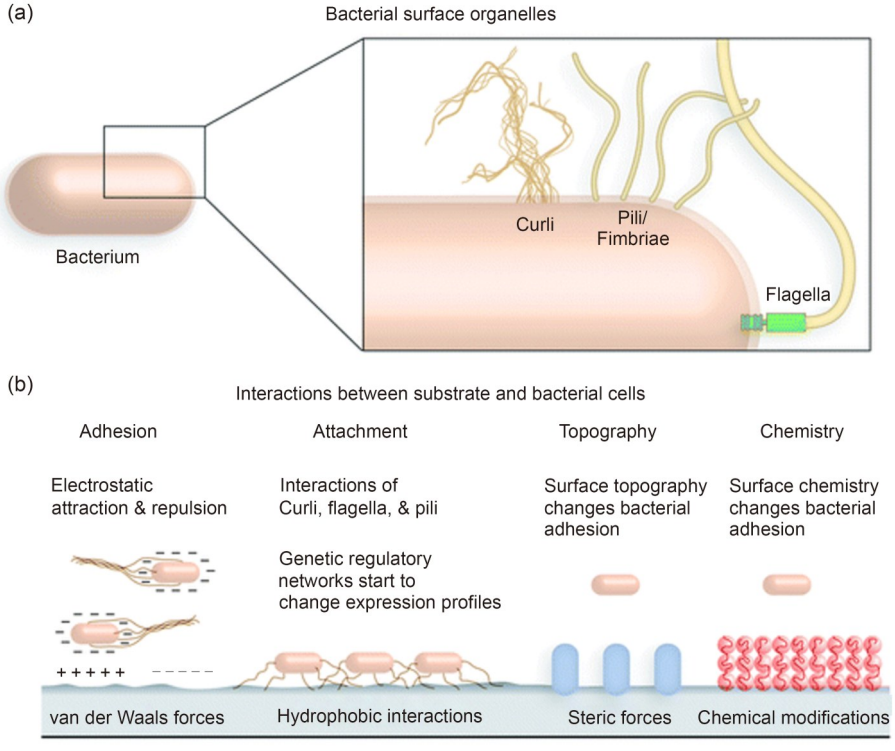


Fig. 2 Mechanisms of bacterial interactions with substrates. (a) The surface organelles of bacteria enable their interactions with substrates. (b) Bacterium–substrate interactions are also influenced by surface properties such as charge, wettability, topography, and exposed chemical groups. Reproduced from [39], with permission from The Royal Society of Chemistry

in the former case, with the bound water layer forming a physical barrier preventing proteins adsorption on the surface [42]. However, superhydrophobic surfaces can resist bacterial adhesion by repelling microorganisms through weak van der Waals forces and an entrapped air layer acting as a barrier [43, 44]. Surface roughness also plays a role in bacterial adhesion as bacteria tend to attach to surface irregularities such as cracks and cavities for protection from undesirable environmental conditions [40].

Bacterial colonization of indwelling medical devices features three stages. Immediately after device insertion, serum proteins adsorb on the surface to form a conditioning film promoting nonspecific bacterial adhesion via hydrophobic, electrostatic, and van der Waals forces [29, 45]. Subsequently, bacterial membrane polysaccharides and proteins specifically interact with the adsorbed proteins through adhesins. Finally, bacteria secrete an extracellular polymeric substance (EPS) matrix to form a mature biofilm [46].

Biofilms are structured bacterial communities embedded in self-produced EPS comprising polysaccharides, proteins, glycolipids, and extracellular deoxyribonucleic acid (DNA). Biofilm development includes the reversible attachment of planktonic bacteria on the surface despite surface repulsion, irreversible attachment via extracellular polymer production and specific adhesins, initial biofilm architecture formation, maturation into a complex structure with continuous EPS production, and release of bacteria from the biofilm into the surrounding environment (Fig. 1) [29, 30].

Biofilms protect pathogenic bacteria from antibiotics and host defense mechanisms, leading to chronic or recurrent infections [34]. Bacteria within biofilms exhibit lower susceptibilities to antibiotics than planktonic forms, often requiring long-term exposure to concentrations up to 1000 times higher to achieve equivalent bactericidal effects [12]. Biofilms are responsible for >80% of human microbial infections and substantially contribute to antibiotic resistance due to slow or inadequate antibiotic penetration and the protected phenotypic state of bacterial subpopulations within the biofilm [45].

2.2.2 Treatment and prevention

The standard treatment for CVC-related infections involves catheter removal or replacement combined with systemic antibiotic therapy [20]. Antibiotics are highly effective at inhibiting bacterial cell wall synthesis by binding to the enzymes responsible for peptidoglycan crosslinking [47]. However, prolonged use can lead to resistance and reduced efficacy over time [48]. Additionally, antibiotic therapies are often ineffective against biofilm-associated infections and further complicated in critically ill patients because of limited vascular access or prolonged infusion requirements [20].

Preventive strategies include the use of maximally sterile barrier techniques during catheter insertion and manipulation, the application of chlorhexidine-releasing dressings, and the continuous education of healthcare workers [3, 11, 49]. Current guidelines recommend the use of catheters impregnated with antimicrobials or antiseptics such as chlorhexidine/Ag sulfadiazine or minocycline–rifampin for CRBSI prevention [11, 49]. Although these catheters are more expensive, their use can potentially decrease overall healthcare costs by preventing infections.

For cases involving long-term CVC use or moderate infection risks, antimicrobial lock therapy is commonly implemented. This technique involves filling the catheter lumen with a high-concentration antimicrobial solution and allowing it to lock to the catheter for a certain period while not in use to target and eliminate microbial biofilms [50]. Common lock agents include vancomycin and heparin, along with antiseptic lock solutions based on ethanol and taurolidine [51].

3 Strategies for CVC bacterial colonization control

The development of materials resisting microbial colonization and biofilm formation is considered a key method of addressing potential shortcomings in clinical practice, with research in this field largely focusing on materials with antifouling and antimicrobial properties [12, 52]. Antifouling (or antiadhesive) materials prevent the surface adhesion of bacteria by repelling them or inhibiting the production of adhesins, thereby resisting initial bacterial attachment. In contrast, antimicrobial materials kill bacteria rather than minimize their deposition, but may have shorter service life. Contact-killing agents compromise the integrity of the bacterial cell membrane and/or inhibit specific metabolic processes, whereas antifouling materials prevent bacteria from adhering to surfaces, thus preventing biofilm formation [47].

3.1 Antifouling materials

Fouling prevention is used to reduce biofilm formation and minimize the risk of CRBSIs and thrombotic complications. Fibrin deposition on the catheter surface, triggered by local venous injury during insertion, can lead to thrombus formation, and thus reduce blood flow and increase the risk of thrombosis. Typically, antifouling materials rely on (i) hydration and/or steric interactions endowed by polyethylene glycol (PEG) derivatives to create a hydrophilic layer that prevents protein adhesion or (ii) incorporate polyzwitterions (such as polysulfobetaine) reducing the formation of conditioning films and thrombosis by forming hydration layers based on electrostatic interactions [53–58]. Francolini et al. [59] showed that modifying PU with PEG markedly reduced *S. epidermidis* adhesion and biofilm formation on the surface, attributing this antifouling effect to an increase

in surface hydrophilicity and the presence of PEG chains at the polymer–water interface. In another work, ZnO NPs obtained via green synthesis from the ethanolic extract of *Eupatorium odoratum* were coated onto commercial totally implantable venous access port surfaces using hydroxypropyl methylcellulose as a binding agent. The resulting hydrophilic coatings inhibited biofilm formation by >97% for *S. aureus* and up to 90% for *E. coli* and *P. aeruginosa* [60].

Surface modification with albumin coatings notably reduces protein adsorption, thus contributing to biofilm formation [52, 61]. However, this effect is relatively transient as albumin is eventually removed upon extended blood contact [62]. Heparin is a systemic agent used to prevent thrombus formation and line occlusion and is therefore a common catheter lock [51]. This agent also effectively hinders nonspecific protein fouling when used as a coating on catheter surfaces. Although heparin is an anticoagulant often used in catheters to prolong their usefulness, it exerts adverse effects upon prolonged use [63].

Low-surface-energy materials such as hydrophobic fluoropolymers (e.g., PTFE) and silicones (e.g., polydimethylsiloxane) can potentially prevent biofilm formation on catheters by minimizing adhesion without the need for extensive surface modification [64]. Although the effectiveness of these materials is debatable, with some studies suggesting that albumin passivation plays a greater role in preventing cell adhesion than the inherent low surface energy, advances in surface topography (e.g., the creation of rough or patterned superhydrophobic coatings) show potential [52]. May et al. [65] showed that an engineered Sharklet micropattern applied to a thermoplastic PU surface notably decreased bacterial adhesion and platelet interactions after simulated vascular exposure. However, the translation of this technique into extra- and intra-luminal catheters to prevent colonization is hindered by cost and manufacturing scalability-related challenges. The consistent creation of large-scale microscale patterns across the catheter surface is technically demanding and may require highly specialized and expensive equipment. Thus, the relationship between surface hydrophobicity and bacterial adhesion is complex and not fully understood. Although some studies suggest that hydrophilic surfaces are generally more resistant to bacterial adherence [41, 66], others indicate that hydrophobicity and superhydrophobicity may exert a stronger influence [43, 44, 64]. These findings highlight the need for a more in-depth analysis on how surface properties affect bacterial behavior in each situation. Current literature suggests that surface characteristics may not act in isolation but rather in conjunction with other factors such as micro- and nanoscale topography, wettability, surface charge, and environmental conditions, highlighting the need for a more integrated approach to understanding bacterial adhesion mechanisms [41, 66]. Besides, additional in vivo studies and clinical evaluations are essential to confirm the long-term effectiveness and stability of these antifouling approaches for widespread implementation in CVC applications.

3.2 Antimicrobial materials

3.2.1 Contact killing

Contact killing strategies focus on the immobilization of antimicrobial agents on the catheter surface to create a lethal barrier preventing microbial colonization [67–69]. The main techniques used to functionalize the catheter interface include plasma grafting, polymerization of biocide-functionalized monomers, covalent bonding, and deposition of insoluble layers. Several contact-killing agents have been explored, such as quaternary ammonium compounds (QACs), guanidine derivatives, antimicrobial peptides (AMPs), and graphene and graphene oxide. QACs and AMPs rely on their cationic nature to disrupt bacterial cell membranes by targeting the phospholipid bilayer [70]. Graphene and its derivatives may disrupt membranes through edge–plane interactions or the in situ generation of reactive oxygen species (ROS) via redox reactions, leading to cytotoxic effects; however, the corresponding mechanisms are debatable [67, 71]. Zander et al. [69] developed a thermoplastic PU (TPU) with an allyl ether side-chain functionality that could be easily surface-modified with the use of antimicrobial agents. Quaternary ammonium thiols (Q*x*-SH) with several hydrocarbon tail lengths were synthesized and attached to the surface using thiol–ene click chemistry. Q8-SH showed the highest effectiveness, enabling rapid contact killing of *S. aureus* and *E. coli* and reducing biofilm formation on prototype catheters. Ribeiro et al. [72] modified CVC tubing by immobilizing core (Fe_3O_4)–shell (aminosilane) NPs functionalized with clavanin A, an AMP. This modification decreased Gram-negative bacteria attachment by up to 90%, and further hyperthermal treatment reduced bacterial viability by 88%. Although the immobilization of antimicrobial agents can prolong their activity because of the stability of surface cationic functional groups, the requirement for direct contact with bacterial cells results in practical limitations. Another disadvantage of such bioactive surfaces is the possibility of their inactivation upon coating by proteins from physiological fluids [12]. Although contact-killing methods provide short-term protection and do not contribute to antibiotic resistance, their effectiveness can be compromised by fouling.

3.2.2 Antimicrobial agent release

Unlike contact killing, antimicrobial agent (biocide) release involves the incorporation of biocidal compounds into the catheter material and their gradual diffusion into the

surrounding environment. Thermally stable antimicrobial agents such as Ag^+ ions or complexes can be uniformly integrated into catheter polymers during thermal processing. Otherwise, catheter surfaces can be exposed to a suitable solvent capable of causing polymer swelling and thereby enabling biocide incorporation at lower temperatures [12]. Despite their effectiveness, drug elution strategies face certain challenges, including limited loading capacity, difficulty in controlling release kinetics, and potential risks of toxicity or allergic reactions [73].

Advanced approaches include surface functionalization or coating with targeted drug delivery systems, bacteriophages, antimicrobial nanomaterials (such as Ag NPs, graphene oxide, and titanium oxide), and natural or synthetic antimicrobial peptides [30, 71]. Despite being promising, many of these innovations remain in preclinical stages, with the corresponding in vivo validations being limited.

Recent studies highlight the feasibility of using these innovations in CVC applications. For instance, niclosamide (NIC)-releasing hot-melt–extruded TPU catheters showed sustained antimicrobial activity and markedly reduced *S. aureus* colonization in vivo [74]. Another approach relies on the grafting of Ag NPs onto catheter surfaces [75, 76]. Mycosynthesized Ag NPs functionalized onto polydopamine-coated CVCs at their minimum bactericidal concentration (31.2 μg/mL) showed strong activity against *A. baumannii*. The modified catheters exhibited a pronounced inhibition zone ((23.9±0.8) mm) and reduced viable bacterial counts by more than three logs. Scanning electron microscopy (SEM) and field-emission SEM analyses revealed near-complete dispersion of biofilms and bacterial lysis, whereas Congo Red agar assays confirmed the absence of black colonies, indicating the total suppression of biofilm-forming capacity [75].

Bacteriophage therapy, particularly the bacteriophage antimicrobial-lock technique, relies on the delivery of high concentrations of lytic phages into catheter lumens, notably reducing bacterial colonization and biofilm formation on CVCs in rabbit models [77, 78]. Raman et al. [79] developed a polyelectrolyte multilayer coating for CVCs to serve as reservoirs for antifungal β-peptides and enabling their controlled intraluminal release. These coatings, fabricated from either polysaccharides (hyaluronic acid/chitosan) or polypeptides (poly-L-lysine/poly-L-glutamic acid), differed in loading and release profiles, with chitosan-based films additionally showing antifungal activity. When loaded with β-peptides, both types of coatings substantially reduced *Candida albicans* colonization and biofilm formation in vitro and in a rat infection model.

Antimicrobial agents can be classified as organic or inorganic. Although many organic antimicrobials are effective against bacteria, they tend to be less stable than inorganic ones, particularly under high temperatures or pressures, featuring higher degradation rates and hence, shorter shelf lives. Inorganic antimicrobials, particularly metals and metal oxides, exhibit the advantages of higher chemical and thermal stability, prolonged shelf-life, and scalability and are therefore suitable for industrial processing and clinical applications [80].

Despite the abundance of studies on novel antimicrobial strategies, few have progressed to clinical trials. Nevertheless, several antimicrobial catheters are already in clinical use. Sect. 3.2.2.1 summarizes key commercial products and their features, with both the products and relevant experimental studies compared in Table 2.

3.2.2.1 Organic antimicrobial agents

Organic antimicrobial agents, including antibiotics and antiseptics, are commonly integrated into catheter polymers or applied as coatings to reduce colonization and CRBSIs. Several antimicrobial CVCs are currently available in the UK and USA (Table 2).

Teleflex, the global market leader in 2020, developed Arrowg+ard® Blue Technology, the first chlorhexidine-based antiseptic coating applied to external catheter surfaces [22]. Its successor, Arrowg+ard® Blue Plus, extends this protection internally, including hubs and extension lines. The bonded coating offers broad-spectrum antimicrobial activity, as revealed by >30 clinical studies [82, 83].

Becton Dickinson, globally ranked second in 2020 after acquiring C.R. Bard, offers the Hydrocath™ catheter (made of PU with a hydrophilic polyvinylpyrrolidone coating mixed with a benzalkonium chloride), complementing its nonantimicrobial portfolio of Hohn®, Hickman®, PowerHohn®, PowerLine®, PowerHickman®, and Trifusion® [22, 92].

Cook Medical held the third position in 2020, featuring a stable acute CVC market share and growth potential. Cook's Spectrum® CVC is impregnated with minocycline and rifampin on both surfaces for infection prevention but is not intended for treating existing infections [22, 85].

B. Braun's Certofix® Protect features a nonleaching coating on internal and external surfaces, a coating that extends from the tip to the connectors [94]. This coating consists of a methacrylate-based polymer that incorporates hydrophilic side groups (such as PEG and the antiseptic polyhexamethylene biguanide (PHMB)) chemically bound to the PU catheter surface; these groups form a positively charged surface that disrupts bacterial cell membranes by damaging their lipid bilayers [73].

Kimal's Altius® ProActiv+, launched in 2015, uses a covalently bound antimicrobial CVC that remains active for up to 30 d even in the presence of blood proteins. This CVC features a patented crosslinked structure that is formed by the copolymerization of PHMB with PEG and creates a positively charged surface attracting and destroying

Table 2 Examples of commercially available antimicrobial polyurethane CVCs, corresponding vendors, product names, antimicrobial agents, action modes, production techniques, and clinical or experimental evidence

Company	Product/Strategy	Antimicrobial agent	Action mode	Protection	Technique	CVC type	Clinical/Experimental evidence	Ref.
Teleflex	Chlorag^{+}ard®	Chlorhexidine	Biocide release	Internal and external surfaces	Coating	Short- and long-term	Not available (NA)	[81]
	Arrowg+ard® Blue	Chlorhexidine/Ag sulfadiazine	Biocide release	External surface	Coating	Short-term	79% CRBSI reduction	[82]
	Arrowg+ard® Blue Plus	Chlorhexidine/Ag sulfadiazine	Biocide release	Intra- and extraluminal	Coating	Short-term	67%–100% reduction in central line-related bloodstream infection	[83, 84]
Cook Medical	Cook's Spectrum®	Minocycline/Rifampin	Biocide release	Internal and external surfaces	Impregnation	Short-term	50% CRBSI reduction	[85]
Edwards Lifesciences Corp	Vantex CVC Oligon	Ag/Pt/C ions (iontophoretic)	Biocide release	Internal and external surfaces	Coating	NA	48% CRBSI reduction	[86, 87]
	AMC Thromboshield treatment	Benzalkonium chloride with heparin coating	Contact killing	Internal and external surfaces	Coating	NA	NA	[12, 88]
Vygon	Multicath Expert	AgION™ (ionized Ag)	Biocide release	Intra- and extraluminal	Impregnation	Short-term	58% colonization reduction	[89, 90]
	Multistar	Rifampicin/Miconazole	Biocide release	Internal and external surfaces	Impregnation	Short-term		[91]
Beckton Dickinson	Hydrocath Assure™	Benzalkonium chloride	Biocide release	NA	Coating	Short-term	NA	[92]
Lepu Medical	Safecath Plus	Minocycline/Rifampicin	Biocide release	Internal and external surfaces	Coating	NA	NA	[93]
B. Braun	Certofix® Protect	PHMB	Contact killing	Internal and external surfaces	Coating	Short-term	NA	[94]
Kimal	Altius® ProActiv+™	PHMB	Contact killing	Catheter inside and outside	Coating	Short-term	NA	[95]
Bactiguard	BIP CVC	Ultrathin layer of Au, Ag, and Pd	Contact killing	NA	Coating	Short- and long-term	52% CRBSI reduction	[96]
Academic studies*	NIC-loaded TPU catheter	NIC	Biocide release	Internal and external surfaces	Impregnation	NA	In vitro *S. aureus* colonization prevention; in vivo biofilm reduction	[74]
	CVC–polydopamine–Ag NPs	Ag NPs	Biocide release	External surface	Coating	NA	>3 log reduction in *A. baumannii* biofilms in vitro	[75]
	QAC-functionalized TPU	QACs	Contact killing	Internal and external surfaces	Coating	NA	>75% reduction in *S. aureus* in vitro and 90% *E. coli* reduction	[69]
	β-Peptide-loaded catheter	β-Peptide	Antifouling/ Biocide release	Internal lumen	Coating	NA	>90% reduction in *C. albicans* colonization and biofilm formation in vitro and in vivo	[79]
	Graphene-based nanoplatelets	Graphene derivatives	Contact killing/ antifouling	Internal and external surfaces	Coating and impregnation	NA	70% reduction in *S. epidermidis* adhesion in vitro; 70% bactericidal activity	[67]
	ZnO NPs synthesized in a green way	ZnO NPs	Antifouling	Internal and external surfaces	Coating	Totally implantable venous access port	>97% inhibition of *S. aureus*; ~90% inhibition of *E. coli* and *P. aeruginosa* biofilms in vitro	[60]

* The lower part of the table shows the experimental strategies, while the upper part shows the commercial products

Gram-positive and Gram-negative bacteria on contact without releasing active agents [95].

Depending on their chemical class, organic antimicrobial agents act through a variety of biochemical pathways. Antibiotics, e.g., minocycline and rifampin, inhibit bacterial growth by disrupting essential processes. Minocycline is a tetracycline antibiotic that binds to the 30S ribosomal subunit and blocks protein synthesis, whereas rifampin inhibits DNA-dependent ribonucleic acid polymerase, preventing transcription [97, 98]. Sulfadiazine, a sulfonamide antibiotic, inhibits folic acid synthesis and thereby impairs nucleic acid production. In combination with Ag and chlorohexidine, as used in Arrowg+ard® Blue Plus catheters, these agents act synergistically to enhance antimicrobial efficacy [99]. Antiseptics, e.g., chlorohexidine and benzalkonium chlorides, primarily interact with the bacterial cell membrane, increasing its permeability and causing cellular content leakage [99]. PHMB exerts a similar effect by binding to negatively charged phospholipids and thus disrupting lipid bilayers and causing cell lysis [100].

The inclusion or coating of antiseptics and antibiotics is the most common strategy available on the antibacterial catheter market. However, the growing threat of antimicrobial resistance, coupled with the limited efficacy of antibiotics against biofilm-associated infections, underscores the urgent need for alternative solutions [16]. Infections derived from resistant bacteria are becoming a major global economic and healthcare concern. Some pathogens have developed resistance to numerous types of antibiotics, with >70% of cases showing resistance to at least one standard antibiotic [101], and antibiotic-resistant infections were responsible for >1.2 million deaths worldwide in 2019 [102]. Thus, effective and affordable antibiotic-free strategies for fighting bacterial infections are urgently required.

Currently, several advances have been made in employing inorganic antimicrobial agents, particularly metal and metal oxide NPs, because of their broad-spectrum antimicrobial activity, high stability, and low toxicity to human cells [16, 103]. Although the related exact antibacterial mechanisms remain under investigation, several theories have been proposed, as discussed in Sect. 3.2.2.2 [16, 36, 104].

3.2.2.2 Inorganic antimicrobial agents

Metals have been used for their antibacterial properties for centuries, the most common of them being Ag because of its bactericidal and bacteriostatic activity at very low concentrations [16]. As mentioned earlier, Ag-based catheter solutions such as Vantex Oligon, AgION™, and Arrowg+ard® Blue are commercially available but expensive [11, 73]. Other metals (e.g., Zn, Au, Ti, and Cu) also exhibit antibacterial properties and can be used in various therapies [16].

Nanotechnology has introduced new possibilities for developing inorganic antimicrobial agents. Metal and metal oxide NPs, including silver oxide (Ag_2O), titanium dioxide (TiO_2), copper oxide (CuO), zinc oxide (ZnO), calcium oxide (CaO), and magnesium oxide (MgO), have been engineered with enhanced antimicrobial properties [16]. Nanomaterials, defined as materials with at least 50% of their constituent particles having one or more external dimensions in the 1–100 nm range [105, 106], have unique properties because of their high surface area-to-volume ratio, which increases with decreasing particle size.

The antimicrobial effects of these NPs are primarily attributed to oxidative stress caused by ROS generation and toxicity due to the release of free metal ions [107]. These actions disrupt bacterial membranes, interfere with intracellular processes, and damage critical cell components such as proteins and DNA. Furthermore, the morphological and physicochemical characteristics of NPs, including size, surface charge, shape, and chemical composition, influence their antimicrobial performance [108].

These mechanisms (Fig. 3) are also applicable to larger particles such as microparticles, and several studies support both hypotheses.

The term "ROS" refers to oxygen-based free radicals with one or more unpaired electrons, e.g., hydrogen peroxide (H_2O_2), superoxide radical ($O_2^{\bullet-}$), and hydroxide radical ($^{\bullet}OH$). These molecules are responsible for diverse biochemical functions and are naturally produced and eliminated in biological systems. However, when ROS levels exceed the capacities of cellular antioxidant defenses, oxidative stress occurs, damaging vital components such as DNA, proteins, and lipids [109, 110]. The cell membrane is particularly vulnerable as ROS can interact with the polyunsaturated fatty acid residues of its phospholipids to generate lipid peroxidation products, generally conjugated dienes and hydroperoxides. These products disrupt the cell membrane and its function, ultimately causing cell death [111]. Lipid peroxidation may also occur inside the cell. Thus, to determine whether the antibacterial effects of NPs are derived from ROS, one can analyze oxidative stress markers and membrane damage in treated bacteria. Sawai [112] used a $ZnCl_2$ solution to reveal that Zn^{2+} ions alone had no effect on *E. coli* or *S. aureus*, whereas ZnO powder with an average particle size of 2.6 μm markedly inhibited growth, indicating that direct contact between ZnO and bacteria is key to expression of antimicrobial activity. In contrast, the same author also reported that ZnO powder in contact with *E. coli* generated H_2O_2 (a 100 mg/mL ZnO slurry produced approximately 50 μg/mL of H_2O_2), identifying this as the reason for the antibacterial activity of ZnO. Similar results were obtained for MgO and CaO powders, as Mg^{2+} and Ca^{2+} did not inhibit *S. aureus* or *E. coli* growth. However, MgO and CaO affected bacterial growth, which was

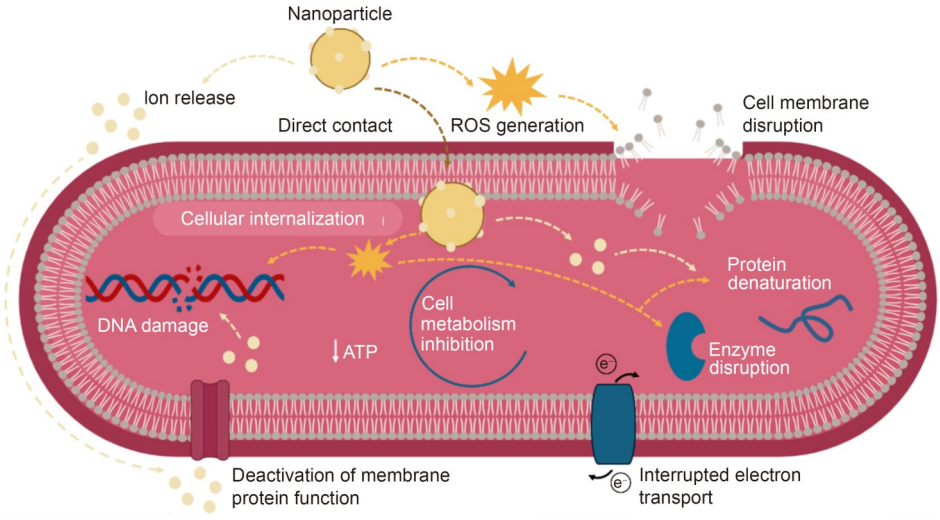


Fig. 3 Antibacterial action mechanisms of NPs. NPs can induce the generation of ROS through several pathways, including interaction with cellular components, redox cycling, and surface-catalyzed reactions. These ROS (e.g., $O_2^{\bullet-}$, $^{\bullet}OH$, and H_2O_2) induce oxidative stress and thus damage bacterial cell membranes, deoxyribonucleic acid, and proteins. Additional effects include the disruption of the electron transport chain and interference with intracellular signaling, ultimately resulting in cell death. ATP: adenosine triphosphate

partially attributed to their hydration-induced alkalinity. Therefore, the author prepared a NaOH solution with an identical pH, revealing that the antibacterial effect in this case was not as strong as that observed for MgO and CaO powders. Therefore, effects other than alkalinity were concluded to be present, and a mechanism involving ROS was proposed for MgO and CaO [112]. Krishnamoorthy et al. [113, 114] linked the antibacterial effect of MgO against *E. coli*, *P. aeruginosa*, and *S. aureus* to lipid peroxidation and the formation of ROS due to the presence of defects or oxygen vacancies at the NP surface. Compared with untreated controls, MgO NPs enhanced ultrasound-induced lipid peroxidation by 129% and 154% at 50 and 100 μg/mL, respectively (P<0.05), which highlights the role of oxidative stress in bacterial inactivation. Das et al. [115] demonstrated that MgO nanoflakes induced intracellular ROS formation in *S. aureus* in a dose- and time-dependent manner. Treatment with 250-μg/mL MgO flakes for 8 h increased ROS levels 2–3-fold compared with the control, with higher concentrations (500–1000 μg/mL) causing a proportionally greater increase in ROS production and leading to cell membrane damage and bacterial inhibition.

The dissolution of metal cations from the surface of metal and metal oxide NPs near or within the bacterial cell is widely regarded as a primary mechanism of their antimicrobial activity. Surface oxidation in suspensions facilitates the generation of soluble ions, with the release rate depending on the susceptibility of the element in question to oxidation [111]. Thus, produced ions can penetrate bacterial membranes and bind to phospholipids, amino acids such as cysteine, and thiol-containing enzymes, leading to enzyme function loss, membrane permeability enhancement, and cellular leakage [111]. In particular, the antimicrobial action of Ag NPs is largely attributed to the release of Ag^+ ions, which readily interact with sulfur- and phosphorus-containing biomolecules such as DNA and proteins, disrupting replication and enzymatic activity [116]. As bacterial membranes are rich in sulfur-containing proteins, Ag^+ ions also target membrane-associated amino acids, impairing viability [34]. In contrast to previous findings, some researchers consider Zn^{2+} ions released from ZnO NPs the major mediators of intracellular bacterial toxicity based on internal cell rupture [117, 118]. Zn^{2+} ions cause bacterial cell death by direct membrane contact, which induces membrane destabilization and permeability enhancement [119], as well as by interacting with nucleic acids and enzymes in the respiratory system, causing enzymatic function disruption [117]. In contrast, although MgO NPs release substantial amounts of Mg^{2+} ions [118], these ions do not exhibit notable toxicity, which indicates a distinct antimicrobial mechanism [118, 120].

However, some authors suggest that antimicrobial effects may also result from structural or mechanical damage to bacterial membranes caused by direct contact with NPs or secondary effects [111]. Dimapilis et al. [121] found the concentrations of Zn^{2+} and H_2O_2 released from ZnO NPs to be too low to explain their strong antibacterial activity, suggesting that this activity is due to NP size. Smaller NPs, owing to their higher surface area-to-volume ratios, interact with bacterial membranes more effectively than larger ones and can penetrate bacterial cell membranes more easily [122]. Grenho et al. [123] demonstrated that ZnO particles with sizes of <50 nm showed stronger bactericidal activities against *E. coli* and *S. aureus* at lower concentrations than larger particles.

Particle size is a key factor determining the antibacterial activity of NPs, as smaller particles can accumulate on bacterial surfaces, possibly through electrostatic interactions. As bacterial membranes carry a negative charge at biological pH because of the presence of carboxylic groups, they strongly bind positively charged NPs, which can result in NP accumulation at the cell membrane and thus cause localized ion release and enhance antimicrobial action [124]. This interaction can cause structural damage by forming pits around NPs and thus increasing permeability, leading to intracellular fluid leakage, disrupting vital transport processes, and ultimately resulting in cell death. NPs may also enter cells via endocytosis and release ions internally, acting as delivery systems [125]. Leung et al. [124] studied the antibacterial activity mechanism of MgO NPs, revealing that they damage *E. coli* membranes without signs of oxidative stress or lipid peroxidation and suggesting an ROS-independent mechanism.

The antibacterial effect of metal and metal oxide NPs also depends on particle shape. Pang et al. [126] assessed the activities of various Cu_2O shapes, such as cubes, octahedra, and hexaspindles, against *Bacillus subtilis*, *S. aureus*, *Enterococcus faecalis* (*E. faecalis*), *Enterobacter cloacae*, and *P. aeruginosa*. Cubic Cu_2O showed consistent bacteriostatic activity across all strains, which was attributed to its surface facets affecting bacterial adsorption and desorption. Similarly, Wang et al. [127] reported that cubic Ag_2O particles were more effective against *E. coli* than octahedral forms at equal concentrations.

The type of metal ion also affects antimicrobial potency. For example, in a study where ZnO, MgO, and CaO powders with similar particle sizes were tested against different bacteria, CaO was most effective against *E. coli*, whereas ZnO was most effective against *S. aureus* [112]. ZnO also outperformed CuO and Fe_2O_3, with Fe_2O_3 NPs showing the least bactericidal action, which suggests that antibacterial efficacy is dependent on the specific metal or metal oxide [128]. CuO NPs with a size of 23 nm exhibited high activity against several bacteria, with *E. coli* and *E. faecalis* being the most susceptible and *K. pneumoniae* showing resistance [129].

Although numerous studies highlight the strong antibacterial properties and stability of metal and metal oxide NPs, their toxicity and accumulation in tissues pose concerns [130, 131]. Furthermore, the potential for bacteria to develop resistance to metal (particularly Ag) compounds remains a debated issue, although conclusive evidence is lacking [132].

However, not all metal NPs have the same toxicity issue. MgO NPs are biodegraded and efficiently metabolized within the body, making them a promising alternative to heavy metal (e.g., Ag)-based NPs. The corresponding degradation products, Mg^{2+} and OH^-, are safely excreted, provided that a normal renal function is maintained [108]. Mg^{2+} is essential for numerous enzymatic reactions and is found in tissues, bones, muscles, and the brain, whereas Mg deficiency has been linked to various health issues. MgO NPs are nontoxic, biocompatible, cost-effective, and harmless [114] and show effectiveness against Gram-positive, Gram-negative, and endospore-forming bacteria, thus being attractive antimicrobial agents [108, 133].

The use of the abovementioned antimicrobial agents should be tailored to specific clinical needs. For catheter applications, surface functionalization or coating with NPs can provide targeted antimicrobial activity while preserving catheter functionality. The development of effective strategies requires the careful selection of NPs, optimization of their concentrations, and thorough toxicity assessment. Moreover, the lack of standardized protocols for the biological evaluation of NPs remains a major challenge. Finally, achieving an optimal balance between antimicrobial activity and biocompatibility, including both cytocompatibility and hemocompatibility, is essential for successful clinical translation.

4 Processing strategies to develop antimicrobial bioactive CVCs

Catheters, made from medical-grade materials, should not trigger coagulation, damage blood components, cause hemolysis, or activate platelets [134, 135] and are commonly fabricated from polymers, especially silicone and PU [53]. Silicone has long been considered the standard because of its biocompatibility, flexibility, and heat resistance. However, the low stiffness, limited tensile strength, and rough surface of silicone increase infection risk [136]. Hence, PU has gained preference because of its superior properties.

PU, synthesized from various sources and highly adaptable, can be thermoplastic or thermosetting. TPU, which is valued for its tunable manufacturing properties and recyclability [137], is prepared from isocyanates and polyols and features urethane linkages and alternating sequences of hard and soft segments [138]. The hard segments, made of aliphatic or aromatic isocyanates and chain extenders, provide toughness and high glass transition temperatures, aiding thermoplastic processing. The soft segments (e.g., polyethers or polyesters) provide elastomeric properties. The nanoscale phase-separated structure of TPUs influences some of their properties [137].

PU is a durable, flexible elastomer with excellent hemocompatibility [139]. Compared with silicone, PU exhibits the benefits of higher tensile strength and easier extrusion, allowing for thinner catheter walls and larger lumen diameters [53, 54]. TPU additionally exhibits the advantages of elasticity, transparency, excellent impact, chemical, and

wear resistance, and shape memory. The properties of TPU can be further tailored by mixing it with other materials or incorporating additives.

Medical-grade TPUs commonly used in CVC manufacturing include Pellethane®, Tecoflex®, and Tecothane® from Lubrizol. A major advantage of TPU is its melt processability, which enables techniques such as extrusion, injection molding, and three-dimensional (3D) printing. TPU can also be processed using non-melt-based methods such as electrospinning, salt leaching, and additive manufacturing (e.g., stereolithography and bioprinting) [137].

Short-term CVCs are commonly made of PU, which provides sufficient rigidity for insertion over a guidewire and facilitates catheter placement. When inserted, the material softens at body temperature, reducing the risk of vessel damage. The high tensile strength of PU enables the creation of multiple thin-walled lumens while maintaining the outer diameter, which increases blood flow rates. Long-term catheters are typically produced from softer silicone to minimize vessel damage and clotting [21], although PU is also used because of its ability to soften within the body [140].

For CVC applications, postinsertion evaluation via noninvasive methods such as X-ray imaging is essential to ensure proper placement and avoid complications such as CRBSI, thrombosis, or vessel perforation. However, conventional polymers, mainly containing C, H, O, and N, are radiolucent because of their low electron density. To address this drawback, radiopaque PUs containing metal salts (e.g., $BaSO_4$) or halogenated (e.g., Br- and I-containing) compounds are often used to fabricate CVCs [141].

4.1 Conventional strategies

Although the manufacturing of antimicrobial CVCs has been extensively researched, many studies fail to provide complete information regarding the employed materials and impregnation processes. This challenge is further exacerbated by the fact that most commercial catheters are patented, which makes understanding the employed impregnation methods difficult, as companies typically do not disclose their precise CVC manufacturing processes, e.g., the details on how the polymer is impregnated or coated with the antimicrobial agent. For example, AgION™ (Table 2) features an ionic Ag antimicrobial agent impregnated into bulk PU [89], with a zeolite used as an ion-exchange matrix. The magnesium aluminosilicate framework of the zeolite is charged with Ag^+ ions, which are then slowly released in exchange for Na^+ ions from the blood [90]. However, the specific impregnation method is not disclosed.

Catheter manufacturing usually involves processes such as injection molding, extrusion, tipping, bonding, and printing. Tipping and bonding are used to produce the Luer lock connector, tip, and side holes of the catheter. During tipping, side holes are drilled into lumens tips, and edges are melted to form a rounded radius and thus minimize the risk of vessel damage. During bonding, luers are attached to catheter extensions through bonding or overmolding. Printing is only used to print useful information on the catheter surface [142]. The impregnation of polymers with antimicrobial agents can be carried out at different stages of material preparation. For antibiotic-impregnated devices, the antibiotic is typically integrated into the bulk material of the device just before injection molding or extrusion [92]. Different processing strategies used to develop antimicrobial CVCs are explored in the following sections (Fig. 4). Their key features, advantages, and limitations are summarized in Table 3.

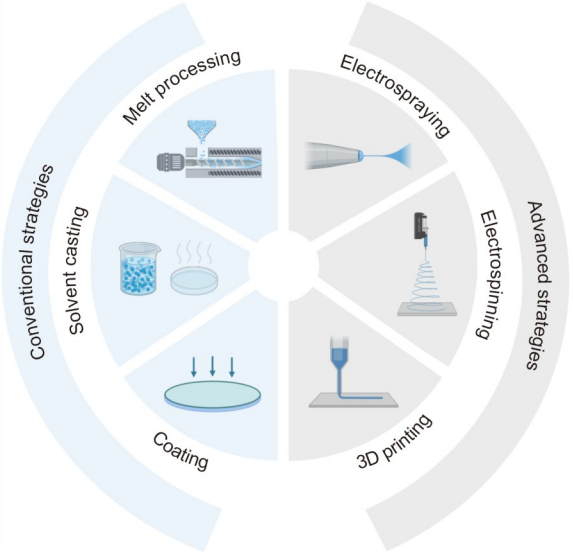


Fig. 4 Overview of the main processing strategies explored for the development of antimicrobial CVCs

4.1.1 Melt processing

Melt processing—a common and efficient technique for processing polymers (especially in large-scale manufacturing)—includes melt mixing, extrusion, and injection molding, and is well suited for producing solid bulk materials from pure polymers or polymer-filled composites. This technique enables the dispersion of antimicrobial particles (such as the widely reported Ag NPs) within the polymer matrix but may not be suitable for materials containing heat-sensitive additives such as antibiotics or certain antioxidants [143].

Injection molding involves melting polymer pellets and injecting the melt into a mold cavity under controlled conditions (e.g., temperature, pressure, and flow rate). Upon cooling, the material solidifies, assuming the shape of the mold. This process is efficient, cost-effective, and ideal for high-volume production with consistent quality and precise

Table 3 Comparison of conventional and advanced strategies for manufacturing antimicrobial CVCs

Strategy	Technique	Key features	Advantages	Limitations
Conventional	Melt processing: extrusion	Polymer is melted and forced through a die to form continuous shapes (e.g., tubes)	Scalability, consistent quality, continuous production	Unsuitability for heat-sensitive agents, limitation to certain geometries
	Melt processing: injection molding	Molten polymer is injected into molds to produce complex shapes	High precision, reproducibility, suitability for complex geometries	Drug degradation at high temperatures, poor suitability for long-shape sections
	Melt processing: melt mixing	Polymer is homogenized with antimicrobial agents before shaping	Uniform distribution of additives, adjustable concentration, versatility for downstream processes	Indirect final product fabrication, need for agents withstanding high temperatures
	Solvent casting	Polymer and antimicrobial are dissolved in a solvent to form thin films or coatings	Simple lab-scale method, possibility of incorporating heat-sensitive agents, moderate potential for uniform drug distribution	Poor scalability, solvent toxicity/disposal issues, risk of particle sedimentation and nonuniformity
	Coating	Antimicrobial agents are applied onto the catheter surface after manufacturing	Versatility, preservation of bulk material properties, adaptability to many antimicrobials	Limited coating durability, risk of delamination or abrasion, need for extra manufacturing step
Advanced	Electrospinning/Electrospraying	Nanofiber meshes with high surface areas, possibility of loading multiple agents	High drug loading potential, tunable release profiles, extracellular matrix mimic	Limited catheter-specific studies, polymer choices that are often unsuitable for CVC use, scalability challenges
	3D printing	Construction of customized geometries	Customized shapes, rapid prototyping, potential for on-demand production	Surface roughness, limited materials for CVC use, regulatory uncertainty, limited long-term durability

tolerances [144]. Injection molding also enables rapid injection cycles of various and complex geometries and is the most widely used method of manufacturing catheter components such as hubs, clamps, suture wings, and Luer connectors [145].

Extrusion is performed for catheter tube production and involves melting the polymer and forcing the melt through a die to create a continuous profile, allowing for precise control over the size, thickness, and other characteristics of the catheter tube. A typical medical tubing extrusion line includes a drying system, an extruder, a die, a cooling tank, a puller (take-up device), and a winder or cutter [146]. Extrusion enables the production of CVCs with different configurations, particularly multilumen profiles with 2–20 lumens and complex lumen geometries including round, star-shaped, elliptical, and crescent-shaped. This process also enables the fabrication of thin walls (thickness: 0.025 mm) and stripped or multilayered coextrusion [147]. Antimicrobial agents typically do not affect the physicochemical behavior of their host polymers during extrusion. However, in the medical device industry, these agents are often incorporated using another compound that is mixed with the polymer prior to the final extrusion.

Melt mixing relies on the combination of two or more materials in a molten state and is commonly used in polymer processing and chemical and pharmaceutical manufacturing. The properties of the resulting blends and composites depend on the structure formed during mixing, as processing parameters such as temperature, material volume, torque, and mixing time influence the blend morphology and particle dispersion. Villani et al. [47] used TPU as a matrix to incorporate Ag, TiO_2, and chitosan during melt compounding. TPU-based composites were prepared using a Brabender electronic plasticorder AEV 153 mixer and then die-cast using a heated plate press at 190 °C, with different pressures used to control product geometry. Unlike Ag and chitosan, TiO_2 caused TPU crystallinity loss when used as a filler and was therefore considered unsuitable for use in catheters or similar applications.

4.1.2 Solvent casting

Other production techniques explored for the development of bioactive catheters include the application of antimicrobial films onto catheter surfaces. These films can be produced by solvent casting, which involves dissolving the polymer and dispersing the inorganic or antimicrobial particles within a solvent. The polymer solution is mixed with a volatile solvent and then cast into a Petri dish, where the solvent is allowed to evaporate to form a polymer film [143]. Thin films of poly(L-lactic acid) with MgO NPs produced using the solvent technique were studied for different biomedical applications [148, 149]. This technique enables the production of approximately 0.2-mm-thick films, which helps to improve antibacterial activity and potentially reproduce CVC walls. Aničić et al. [150] developed an antimicrobial polymeric composite containing nanotextured MgO using biodegradable polymer matrices, namely,

poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL). The composites were produced via solvent casting, and the MgO/PLGA composite showed optimal polymer degradation kinetics, enhancing bactericidal activity against planktonic *E. coli* and sessile bacteria such as *S. epidermidis*, *S. aureus*, and *P. aeruginosa.* This composite was also capable of controlled Mg^{2+} release without harming red blood cells and was more effective against bacteria than PCL or PLA analogs because of differences in the corresponding polymer degradation rates, MgO microrod distributions, and interaction strength. Although the authors mentioned the development of composites by solvent casting, this technique holds promise for coating catheters and other medical devices as the employed polymers are biodegradable. However, a disadvantage of this process is the use of organic solvents, which raises environmental and disposal concerns. In addition, the process lacks scalability for industrial applications, and the deposition of larger particles during casting may cause a nonuniform particle distribution in the film. Hence, realizing a uniform particle distribution throughout the sample thickness may be required in some cases, and cast films may require postprocessing through hot-pressing [143].

Vazquez-Rodriguez et al. [74] developed an antibacterial catheter by incorporating NIC, an anthelmintic drug, into a TPU matrix at 2%, 5%, and 10% (w/w) using solvent casting and hot-melt extrusion. NIC was suspended in chloroform, and the suspension was sonicated and stirred for 30 min to ensure a homogeneous NIC distribution. TPU was added to the mixture upon stirring at a loading of 12.5% (0.125 g/mL), and stirring was continued overnight to dissolve the polymer. The solution was cast into a 200-mm-diameter Petri dish to evaporate chloroform, and the resulting films were vacuum-dried for 3 d at 25 °C and 50 mbar (1 mbar=100 Pa) (Fig. 5a), cut into strips, and fed into a single-screw extruder with a 0.8-mm-diameter stainless steel nozzle or 3D-printing coaxial nozzle (Fig. 5b). Extrusion was performed at 180 °C at a screw speed of 75 r/min. Catheters loaded with NIC experienced notably reduced biofilm formation and planktonic bacterial growth, particularly for *S. aureus*, with minimal bacterial adhesion observed by SEM for the 2% and 5% (w/w) NIC-loaded segments (Figs. 5c–5e).

4.1.3 Coating

Dip coating (or immersion) is widely used in laboratory and industrial settings because of its simplicity, adaptability to various substrate shapes, adjustable coating thickness, cost-effectiveness, and reproducibility [151]. In this process, the substrate is immersed into a solution containing antimicrobial agents (metal compounds or particles) and then withdrawn at a steady rate to create a uniform liquid film on the surface. Solvent evaporation and chemical reactions occurring during drying provide a thin coating [152]. This process is influenced by various factors (e.g., immersion time, withdrawal speed, number of cycles, solution viscosity, temperature, surface tension, and gravitational and inertial forces), each of which can affect coating uniformity, thickness, and overall quality [151]. Several studies have used dip coating to develop antimicrobial CVCs, especially coating catheters with Ag NPs [75, 153–155]. In the study by Thomas et al. [153], the CVC (Teleflex) was cut into 1 cm×1 cm segments, which were then immersed into an Ag NP suspension (50 μg/mL) for 24 h. Subsequently, the excess suspension was carefully removed by blotting, and the segments were dried at 50 °C. Microbially synthesized (MAgNPs) and photosynthesized Ag NPs (CAgNPs) were used. Compared with the uncoated CVC, the CVC coated with MAgNPs at a concentration of 50 μg/mL reduced *S. aureus* biofilm formation by 94.8%, whereas a reduction of 92.2% was achieved for CAgNPs. In another study, silicone tubes were coated with an adherent hydrophilic polymer comprising a polyelectrolyte, nonionic hydrophilic polymer, and Ag NPs (8% or 15% by dry mass) using dip coating followed by ultraviolet radiation curing and were compared with commercial CVCs [154, 155]. As mentioned above for the impregnation process, many antimicrobial catheter coating methods do not disclose complete information regarding the procedures involved. The fabrication of the patented Bactiguard® coating involves a series of controlled dipping steps in metal solutions containing Ag, Au, and Pd to create a submicron metal layer firmly adhering to the PU catheter surface. The coating metal composition was optimized for anti-infective properties and blood compatibility, and no notable release was observed during use [156]. Gendine-coated peripherally inserted central catheters (PICCs) were produced by applying a patented sequential coating process to a PU catheter after extrusion. This process incorporates gendine (a mixture of gentian violet and chlorhexidine) onto luminal and external surfaces [157]. Sequential coating was also used in other studies. CVC segments (4 cm in length) were immersed in a chlorhexidine solution (40 mg/mL) for 4 h and then impregnated with a minocycline (15 mg/mL)–rifampin (30 mg/mL) mixture for 1 h. After impregnation, the catheters were air-flushed to remove the excess coating solution from the lumens, dried overnight at 55 °C, rinsed with water, and dried again [158]. In contrast, a subsequent study used the same combination of agents but applied them in reverse order. The PU used for CVC production was impregnated with a minocycline–rifampin mixture; chlorhexidine was then applied to the lumen and external surfaces, and the material was dried. This updated method resulted in a smoother surface finish of the coated catheters and has been licensed to Cook® Medical [159, 160]. Dip coating was used to obtain a chitosan-based coating on silicone catheters. Catheter

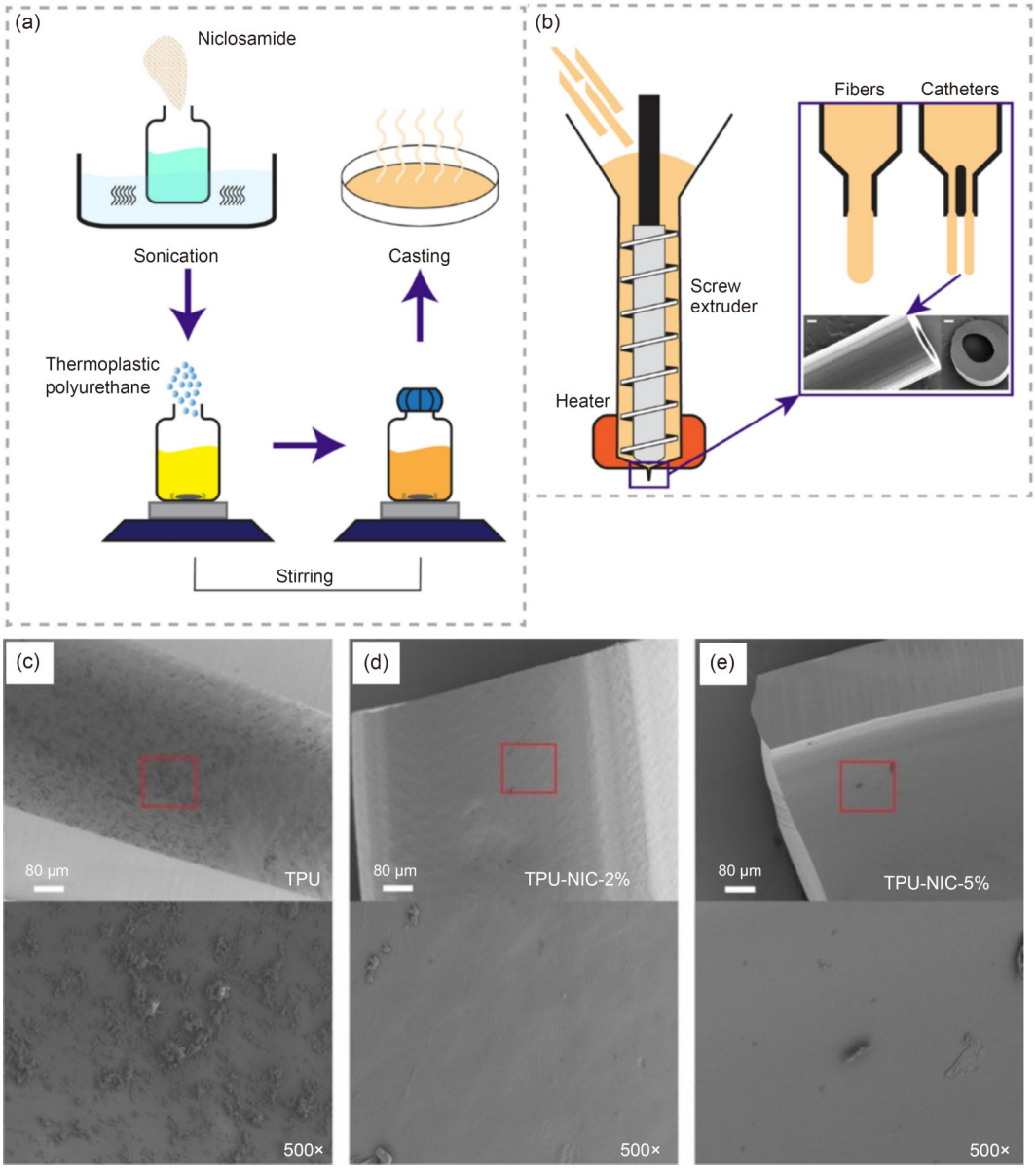


Fig. 5 Production processes and biofilm assessment of NIC-loaded TPU catheters. (a) Fabrication of NIC-loaded TPU via solvent casting. (b) Fiber and catheter production using hot-melt extrusion (scale bars: 200 μm). (c–e) Scanning electron microscopy (SEM) images of surface-attached methicillin-sensitive *S. aureus* biofilms formed after 24 h. Top (100× magnification) and bottom (500× magnification) rows show images of longitudinally sectioned catheter segments, revealing intraluminal bacterial colonization on (c) pristine TPU and (d) 2% (w/w) and (e) 5% (w/w) NIC-loaded TPU. Reproduced from [74], licensed under CC BY 4.0

tubes (external diameter: 4 mm) and 3D-printed reservoir-implanted ports were dipped in a chitosan solution, with subsequent solvent evaporation resulting in film deposition. The catheters were coated with or without prior oxygen-plasma treatment and dipped in an alginate solution. However, the addition of alginate and/or plasma treatment did not improve antibacterial efficiency [161]. Ribeiro et al. [72] applied plasma treatment to silicone catheter tubing as a step preceding CVC modification. After 5 min of plasma treatment, the catheter was immersed in a 0.1 mol/L solution of (3-aminopropyl)triethoxysilane in anhydrous ethanol overnight to expose primary amino groups at the surface. After rinsing with ethanol and nitrogen-drying, the substrates were sequentially immersed in 2.5% glutaraldehyde, Fe_3O_4 NPs functionalized with dimercaptosuccinic acid (DMSA), and antimicrobial peptide (clavanin) solutions to afford Fe_3O_4-DMSA-clavanin-functionalized CVCs. Dip coating was used alongside spin coating to deposit a dispersion containing silicone rubber with oxidized and nonoxidized graphene nanoplatelets (GNPs) onto silicone surfaces. Spray coating achieved the complete surface coverage of silicone films with GNPs, while dip coating provided a

lower GNP coverage but led to more effective particle immobilization [68].

Liu et al. [162] developed a multifunctional coating complex by assembling heparin sodium (HS) and an organosilicon quaternary ammonium surfactant, dimethyloctadecyl[3-(trimethoxysilyl)propyl] ammonium (DAC), to prevent CRBSI and catheter-related thrombosis. When applied to intravascular catheters via sequential dipping, the coating achieved an antibacterial efficacy of >97% and reduced thrombus adhesion by 60% in vitro and in vivo. Figure 6 illustrates the abovementioned coating process and application to CVCs.

4.2 Advanced strategies

4.2.1 Electrospinning and electrospraying

Electrospinning, which has been explored as an alternative to conventional approaches for bioactive biomedical applications, involves the production of fibers under a high electric field. Under these conditions, polymer fluids are electrostatically atomized into fine jets that solidify into fibers with diameters ranging from several nanometers to submicrometers [163, 164]. Electrospun meshes have high surface areas and porosities and can mimic the extracellular matrix, thus being ideal for tissue engineering, wound healing, and controlled drug release [164]. Although these meshes are mainly used in applications that require structural support to promote tissue regeneration, they can also be used to produce membranes for catheter applications [165–167]. Xu et al. [166] created bifunctional PLA-based membranes incorporating black phosphorus nanosheets and ZnO NPs using electrospinning to improve the biocompatibility and antibacterial properties of catheter materials. Another study used electrospinning to coat catheters with nanofibers and thus enable the capture and elimination of circulating tumor cells via irreversible electroporation; however, these catheters were not intended for antibacterial use [168]. Electrospraying has also been used to deposit silica onto polyethylene terephthalate films and thus create antiadhesive surfaces with potential catheter applications [169]. However, most studies have not directly tested these approaches in catheter models, and the employed polymers are generally unsuitable for CVC applications. Although electrospinning- and electrospraying-based strategies for the development of antimicrobial CVCs are rarely found in literature, they hold promise for the future development of antimicrobial coatings for catheters.

4.2.2 3D printing

3D printing is an additive manufacturing technology that produces layer-by-layer 3D objects from a computer-aided design model and allows one to incorporate drugs directly into the structure of a device or construct itself. Several studies used 3D printing for catheter preparation. In their in vitro proof-of-concept study, Weisman et al. [170] used fused deposition modeling (FDM) to create a customized bioactive catheter loaded with antibiotics and chemotherapeutics for potential use in interventional radiology. The authors placed bioplastic (PLA) pellets coated with powdered gentamicin sulfate (GS; 1 wt%) or methotrexate (MTX; 2.5 wt% and 5 wt%) into a vortex mixer and extruded the mixture to produce filaments. A 14-F catheter tip was produced using an FDM 3D printer with a layer height of 300 μm using GS- and MTX-loaded filaments (Figs. 7a and 7b). The 3D-printed catheters showed an initial burst release followed by sustained drug release for 5 d in simulated body fluid. The catheters containing GS inhibited bacterial growth in broth cultures (average inhibition area: (858 ± 118) mm^2), whereas control catheters showed no antibacterial effect [170]. Although this study revealed an antimicrobial effect due to antibiotic release, this effect lasted only several days. Additionally, the design and larger dimensions of the produced catheter, along with the surface topography resulting from the layer-by-layer deposition technique used in FDM, led to surface roughness and irregularities that were not compliant with the ideal characteristics expected of catheter surfaces. Moreover, the study did not explore the use of materials commonly employed in catheter manufacturing, such as PU or silicone. This is an important limitation for this application, as using PLA-based materials in patients is challenging because of the rigidity of this polymer. As drug diffusion typically occurs on the surface of biodegradable polymers, this characteristic may be different from that of the nonbiodegradable polymers commonly used in catheter production. As noted by the authors, these findings are preliminary and serve as a proof of concept, indicating that further methodology improvement is needed to develop a fully functional catheter.

Mathew et al. [63] also used FDM 3D printing to develop an antimicrobial catheter made of TPU containing tetracycline hydrochloride (TC). The authors prepared filaments with different TC loadings (0, 0.25 wt%, 0.5 wt%, and 1 wt%) by coating TPU pellets with castor oil in a vortex mixer, adding TC, and processing the mixture in a filament extruder at 170–190 °C (Figs. 7c and 7d). 3D-printed catheters with external and internal diameters of 5 and 2 mm, respectively, as well as square specimens measuring 10 mm×10 mm×1 mm, were produced using a fused filament fabrication (Ultimaker 3) system with a 0.4-mm-diameter nozzle and a layer height of 0.1 mm. The drug release profile of the catheters showed an initial burst followed by a plateau, with 1 wt% TC catheters releasing more TC even after 10 d of incubation in phosphate-buffered solution. All TC-containing specimens inhibited the growth

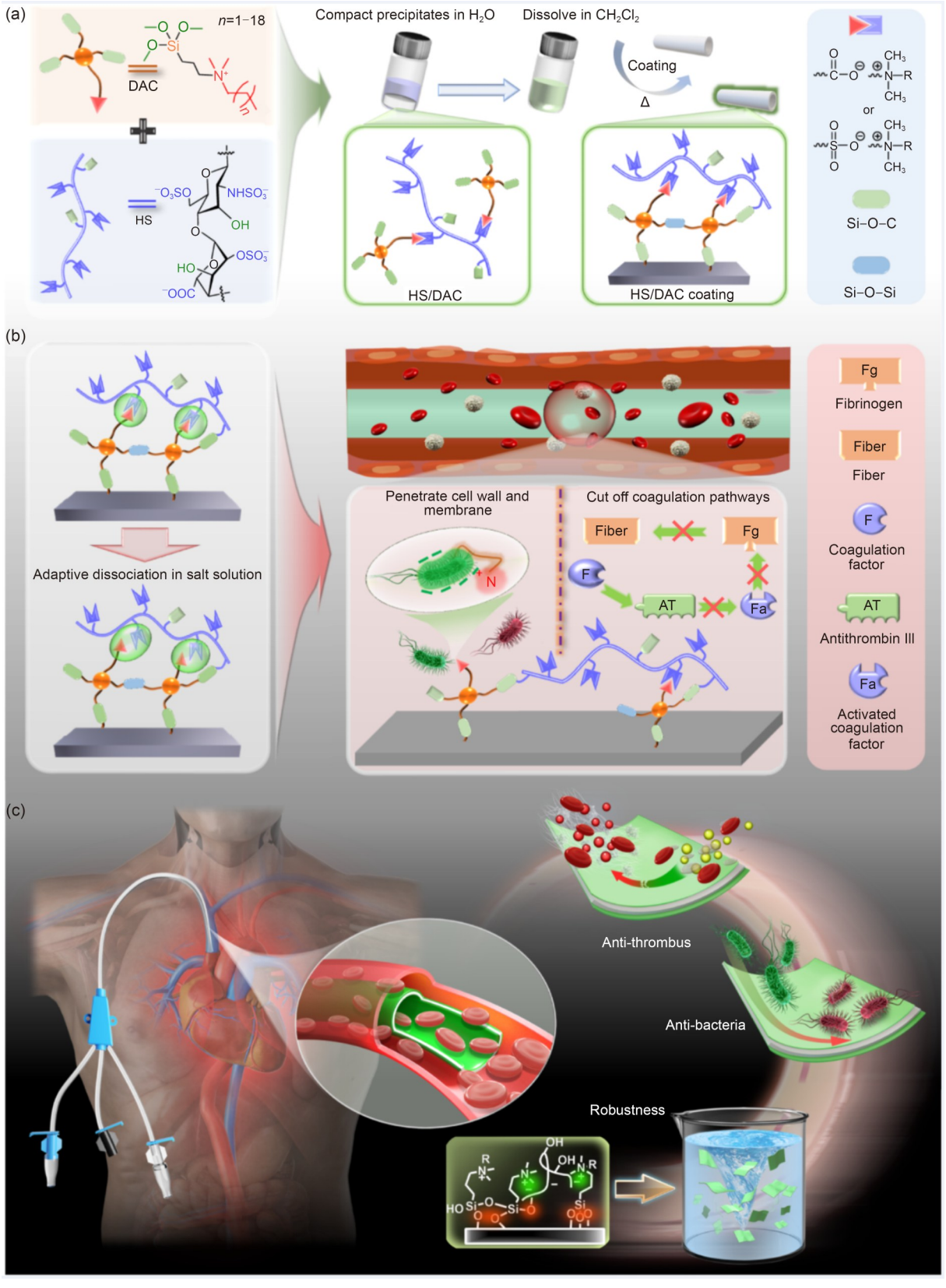


Fig. 6 Development and evaluation of multifunctional coatings for CVCs. (a) Schematic preparation of HS/DAC complex and its application as a coating. (b) Dissociation behavior of HS/DAC coatings and their antibacterial and antithrombotic properties. (c) Multifunctionality of HS/DAC-coated CVCs, which combine durability with antibacterial and antithrombotic performance. Reproduced from [162], licensed under CC BY 4.0

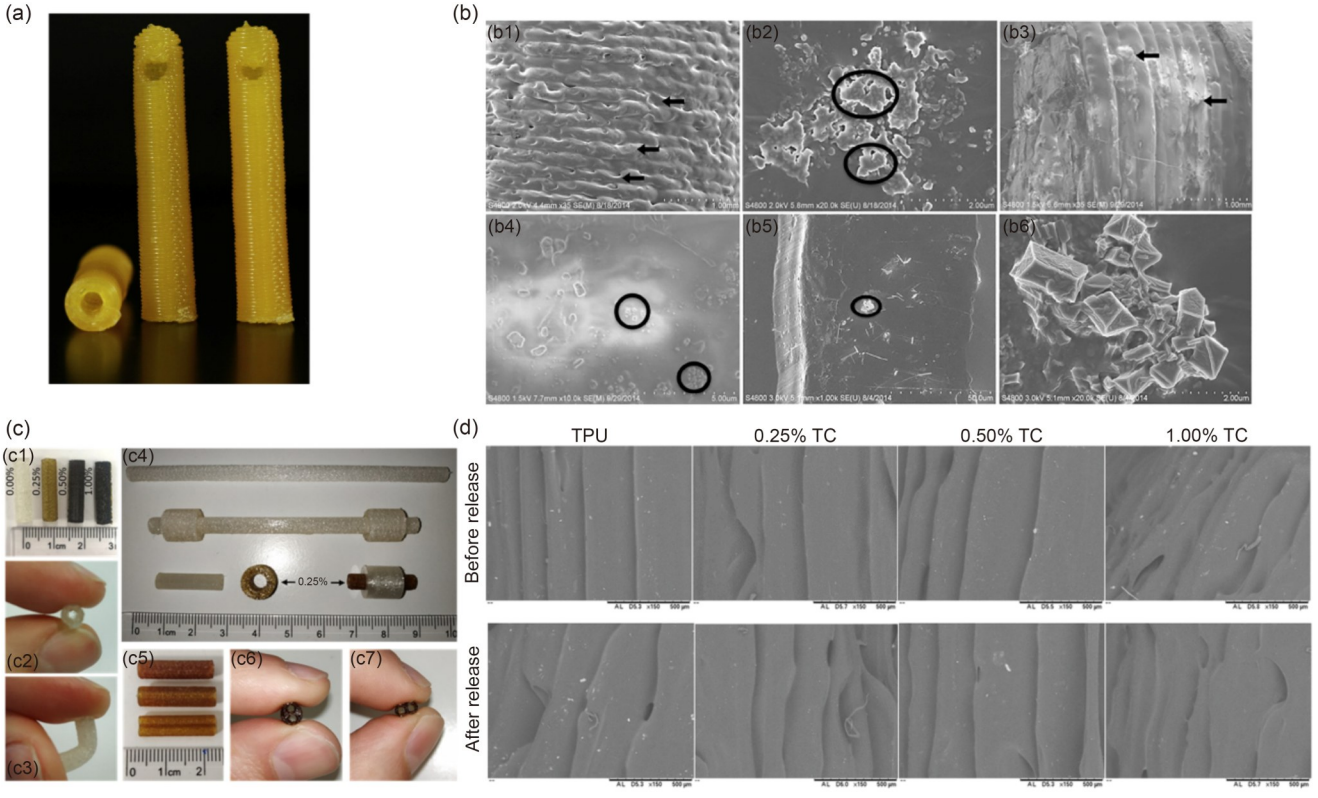


Fig. 7 Fabrication and characterization of antibiotic and chemotherapeutic eluting 3D-printed catheters for interventional radiology. (a) 3D-printed catheters containing MTX. (b) SEM images of catheters with (b1, b2) gentamicin- and (b3, b4) MTX-loaded filaments at magnifications of (b5) 1000× and (b6) 20 000×. Amorphous defects observed at a magnification of 35× suggest gentamicin integration (b1, arrows), as confirmed by the amorphous gentamicin structure observed at a magnification of 20 000× (b2, circles). Rough protrusions on the catheter surface at a magnification of 35× suggest MTX incorporation (b3, arrows), with crystalline clusters observed at a magnification of 10 000× (b4, circles). Reproduced from [170], with permission from The Association of University Radiologists. (c) 3D-printed antimicrobial catheters: (c1–c3) catheters printed with 0, 0.25 wt%, 0.5 wt%, and 1 wt% TC; (c4) longer catheters with and without cuffs and spare-printed cuffs with and without antibiotics; (c5–c7) different catheter designs. (d) SEM images of TC-loaded 3D-printed catheters before and after release experiments (scale bars: 500 μm). Reproduced from [63], with permission from the American Chemical Society

of *S. aureus*, with the most pronounced effect observed at the highest TC loading. This highest-loading catheter maintained its antibacterial activity for up to 10 d, which suggested potential for even longer effectiveness, as only 4% of the drug was released at that time.

4.3 Challenges in clinical translation

The emergence of new CVC technologies, including antimicrobial strategies such as antibiotic or antiseptic coatings, impregnated catheters, and inorganic NPs, has the potential to improve patient safety and expand CVC use in diverse healthcare applications. However, these advances face critical challenges. Although antimicrobial and biocompatible materials can reduce infection rates, the high risk of CRBSI, antibiotic resistance, biofilm formation, and thrombosis and rigorous regulatory requirements hinder clinical translation. The complexity of upscaling some strategies for industrial use and the high cost of advanced catheter technologies also limit accessibility and implementation.

Extrusion, a highly specialized process widely used in CVC tube manufacturing, is often hindered by factors such as temperature settings, material contamination, and equipment design. Common problems such as surging (variation in product thickness), bubbles, rough surfaces, and inconsistent gauge control are typically due to high moisture content, incorrect temperature, or incompatible additives [147]. The addition of antimicrobial agents to the material to be extruded aggravates these challenges as these agents may affect process stability and product quality. Therefore, antimicrobial agents should be carefully chosen to ensure process efficiency and final product integrity. For example, as extrusion and other melt processing techniques involve high temperatures, these agents must be thermoresistant. Organic agents, which are often unstable at high temperatures, may degrade during extrusion and are therefore poorly suited for such processes [80, 143].

Some alternatives have been suggested, e.g., inorganic agents (particularly NPs), which are thermally stable and effective at low concentrations [80]. However, the frequent

use of Ag and heavy metals raises concerns regarding toxicity, resistance, and environmental impact. Exploring alternative inorganic agents with a focus on biocompatibility could help address these issues and combat the increasing resistance to commonly used antimicrobial therapies. Additionally, standards for the validation of antimicrobial NPs need to be established to improve the reproducibility and reliability of these approaches.

The impregnation methods currently used to produce antimicrobial CVCs present limitations, particularly in maintaining distribution homogeneity, controlling the release rate of antimicrobial agents, and ensuring compatibility between the agents, catheter materials, and manufacturing processes. Coating is often applied as an alternative strategy after conventional manufacturing to overcome these limitations and may enable more controlled and customized release while maintaining catheter structural integrity. The durability of antimicrobial coatings is another key challenge for clinical translation. In real-world use, catheters are exposed to repeated handling, mechanical abrasion, sterilization, and prolonged contact with body fluids, all of which can accelerate coating degradation or delamination. Coating adhesion and uniformity are critical to maintaining functionality, particularly for long-term indwelling devices. Addressing these durability issues requires optimized surface preparation, robust bonding techniques, and thorough validation under clinically relevant mechanical and chemical stresses, as well as standardized durability testing protocols, to ensure reproducible and reliable performance.

Advanced strategies such as 3D printing also hold promise for the manufacture of antimicrobial catheters, offering the benefits of rapid prototyping, low cost of small-scale implementation, flexibility, fast production, and customizability [63, 170]. However, current 3D printing technologies present notable limitations in surface finish, structural precision, and the ability to reproduce complex catheter geometries with multiple lumens, narrow and long bores, and thin walls. The irregular surface of 3D-printed catheters can compromise material integrity and biocompatibility. Moreover, the remaining regulatory concerns regarding the use of 3D printing in the production of medical devices [171] require further technological and material advancements to meet clinical standards.

Collaboration between research institutions, hospitals, and industry, as well as flexible adaptation to evolving market needs, is essential for the development and adoption of antimicrobial catheters. Overcoming these barriers through continued innovation and cost-effective solutions is critical to fully achieve the potential of advanced antimicrobial catheter technologies to improve patient outcomes.

5 Conclusions and future trends

CVCs are crucial medical devices designed to access central venous circulation and used to manage critical clinical conditions. However, CVC insertion under urgent conditions as well as frequent handling increases susceptibility to microbial colonization. Once bacteria adhere to a CVC and form a biofilm, they become shielded from the surrounding environment, becoming less susceptible to antibiotic therapy and therefore very difficult to eradicate. CRBSIs remain a major cause of morbidity and mortality, often requiring catheter removal and leading to increased healthcare costs and risks.

Current clinical strategies aiming to prevent such infections, including the use of catheters coated or impregnated with antibiotics or antiseptics, are largely ineffective against established biofilms. Moreover, the growing threat of antibiotic-resistant bacteria highlights the urgent need for alternative antibiotic-free solutions. Innovative approaches such as the incorporation of antimicrobial peptides and NPs, as well as surface functionalization, are being actively studied, although few have progressed to clinical trials.

Among these, inorganic materials such as metal and metal oxide NPs exhibit promising antibacterial properties because of their broad-spectrum activity, stability, and safety. Although the corresponding activity mechanisms require further investigation, the nanoscale design of these species enables effective bacterial targeting with minimal harm to human tissues.

Future efforts should focus on these materials for catheter applications as they have the potential to markedly enhance infection control and provide durable alternatives to organic agents. A deeper understanding of their antimicrobial mechanisms and optimization of physicochemical properties will be key to designing effective and bioactive catheters. Furthermore, the chosen fabrication strategies must support industrial scalability to enable clinical translation.

From this perspective, this review aims to guide future innovations in antimicrobial catheter technologies, emphasizing preventive strategies that inhibit bacterial colonization and subsequent biofilm formation.

Acknowledgements This work was financially supported by the Foundation for Science and Technology (FCT) under the project CDRSP funding (DOI: 10.54499/UID/04044/2025 and ARISE funding (DOI: 1054499/LA/P/0112/2020); the grant awarded to TP (10.54499/2020.09198.BD); and the funding to JRD (10.54499/CEECINST/00060/2021/CP2902/CT0005). This study was also supported by INOV.AM – Inovação em Fabricação Aditiva, 02-C05-i01.01-2022 and Nanofilm (CENTRO2030-FEDER-01469100). Support was also received from i3S.

Author contributions TP: conceptualization, methodology, investigation, visualization, writing—original draft, and writing—review and editing. FJM: conceptualization, funding acquisition, resources, supervision, validation, and writing—review and editing. SRS:

conceptualization, funding acquisition, resources, supervision, validation, and writing—review and editing. JRD: conceptualization, funding acquisition, resources, supervision, validation, and writing—review and editing.

Funding Open access funding provided by FCT|FCCN (b-on).

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

Use of generative AI tools The authors used ChatGPT to assist with reducing word count. All content was reviewed and edited by the authors, who take full responsibility for the manuscript.

References

1. Shrivastava A, Singh S, Taank P et al (2021) Incidence, risk factors, and microbiology of central venous catheterization-associated bloodstream infections at a surgical tertiary intensive care unit. *J Sci Soc* 48(1):28–32. https://doi.org/10.4103/jss.jss_68_20
2. Berardi R, Rinaldi S, Santini D et al (2015) Increased rates of local complication of central venous catheters in the targeted anticancer therapy era: a 2-year retrospective analysis. *Support Care Cancer* 23(5):1295–1302. https://doi.org/10.1007/s00520-014-2466-y
3. O'Grady NP (2023) Prevention of central line-associated bloodstream infections. *N Engl J Med* 389(12):1121–1131. https://doi.org/10.1056/NEJMra2213296
4. Micic D, Semrad C, Chopra V (2019) Choosing the right central venous catheter for parenteral nutrition. *Am J Gastroenterol* 114(1):4–6. https://doi.org/10.1038/s41395-018-0203-8
5. Percival SL, Suleman L, Vuotto C et al (2015) Healthcare-associated infections, medical devices and biofilms: risk, tolerance and control. *J Med Microbiol* 64(4):323–334. https://doi.org/10.1099/jmm.0.000032
6. Khan HA, Baig FK, Mehboob R (2017) Nosocomial infections: epidemiology, prevention, control and surveillance. *Asian Pac J Trop Biomed* 7(5):478–482. https://doi.org/10.1016/j.apjtb.2017.01.019
7. Becerra-Bolaños Á, Domínguez-Díaz Y, Trujillo-Morales H et al (2025) Assessing infection related to short-term central venous catheters in the perioperative setting. *Sci Rep* 15:1642. https://doi.org/10.1038/s41598-025-85836-z
8. Gahlot R, Gahlot R, Nigam C et al (2014) Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci* 4(2):162. https://doi.org/10.4103/2229-5151.134184
9. Pérez-Granda MJ, Guembe M, Cruces R et al (2016) Assessment of central venous catheter colonization using surveillance culture of withdrawn connectors and insertion site skin. *Crit Care* 20(1):32. https://doi.org/10.1186/s13054-016-1201-0
10. Haddadin Y, Annamaraju P, Regunath H (2022) Central Line-Associated Blood Stream Infections. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK430891/ [Accessed on 30 April 2025]
11. O'Grady NP, Alexander M, Burns LA et al (2011) Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 39(4):S1–S34. https://doi.org/10.1016/j.ajic.2011.01.003
12. Casimero C, Ruddock T, Hegarty C et al (2020) Minimising blood stream infection: developing new materials for intravascular catheters. *Medicines* 7(9):49. https://doi.org/10.3390/medicines7090049
13. Centers for Disease Control and Prevention (2011) Vital signs: central line-associated blood stream infections—United States, 2001, 2008, and 2009. *MMWR* 60(8):243–248. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6008a4.htm
14. Zhong YY, Zhou LM, Liu XL et al (2021) Incidence, risk factors, and attributable mortality of catheter-related bloodstream infections in the intensive care unit after suspected catheters infection: a retrospective 10-year cohort study. *Infect Dis Ther* 10(2):985–999. https://doi.org/10.1007/s40121-021-00429-3
15. Ahn HM, Kim JS, Park MG et al (2023) Incidence and short-term outcomes of central line-related bloodstream infection in patients admitted to the emergency department: a single-center retrospective study. *Sci Rep* 13(1):3867. https://doi.org/10.1038/s41598-023-31100-1
16. Dizaj SM, Lotfipour F, Barzegar-Jalali M et al (2014) Antimicrobial activity of the metals and metal oxide nanoparticles. *Mater Sci Eng C* 44:278–284. https://doi.org/10.1016/j.msec.2014.08.031
17. de Grooth HJ, Hagel S, Mimoz O (2024) Central venous catheter insertion site and infection prevention in 2024. *Intensive Care Med* 50(11):1897–1899. https://doi.org/10.1007/s00134-024-07664-5
18. Hill B, Smith C (2021) Central venous pressure monitoring in critical care settings. *Br J Nurs* 30(4):230–236. https://doi.org/10.12968/bjon.2021.30.4.230
19. Akaraborworn O (2017) A review in emergency central venous catheterization. *Chin J Traumatol* 20(3):137–140. https://doi.org/10.1016/j.cjtee.2017.03.003
20. Böll B, Schalk E, Buchheidt D et al (2021) Central venous catheter-related infections in hematology and oncology: 2020 updated guidelines on diagnosis, management, and prevention by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol* 100(1):239–259. https://doi.org/10.1007/s00277-020-04286-x
21. Hudman L, Bodenham A (2013) Practical aspects of long-term venous access. *Continuing Educ Anaesth Crit Care Pain* 13(1): 6–11. https://doi.org/10.1093/bjaceaccp/mks039
22. iDataResearch (2021) Central Venous Catheter Market Size, Share & Trends Analysis | Global | 2020–2026 | MedCore | Segmented by: Product Type (Acute/Chronic, Power-Injectable, Conventional, and Antimicrobial CVCs).

https://idataresearch.com/product-category/cardiology/vascular-access [Accessed on 30 December 2024]
23. Reports and Data (2025) Central Venous Catheters Market. https://www.reportsanddata.com/report-detail/central-venous-catheter-market [Accessed on 27 February 2025]
24. FMI (2024) Central Venous Catheter Market. https://www.futuremarketinsights.com/reports/central-venous-catheter-market [Accessed on 30 November 2024]
25. Zhang YB, Wang YC, Sheng ZK et al (2023) Incidence rate, pathogens and economic burden of catheter-related bloodstream infection: a single-center, retrospective case-control study. *Infect Drug Resist* 16:3551–3560. https://doi.org/10.2147/IDR.S406681
26. Brunelli SM, Turenne W, Sibbel S et al (2016) Clinical and economic burden of bloodstream infections in critical care patients with central venous catheters. *J Crit Care* 35:69–74. https://doi.org/10.1016/j.jcrc.2016.04.035
27. Kern WV (2017) Infections associated with intravascular lines and grafts. In: Cohen J, Powderly WG, Opal SM (Eds.), Infectious Diseases. Elsevier, p.427–438. https://doi.org/10.1016/b978-0-7020-6285-8.00048-4
28. Mermel LA (2011) What is the predominant source of intravascular catheter infections? *Clin Infect Dis* 52(2):211–212. https://doi.org/10.1093/cid/ciq108
29. Zhao AL, Sun JZ, Liu YP (2023) Understanding bacterial biofilms: from definition to treatment strategies. *Front Cell Infect Microbiol* 13:1137947. https://doi.org/10.3389/fcimb.2023.1137947
30. Beloin C, Fernández-Hidalgo N, Lebeaux D (2017) Understanding biofilm formation in intravascular device-related infections. *Intensive Care Med* 43(3):443–446. https://doi.org/10.1007/s00134-016-4480-7
31. Timsit JF, Dubois Y, Minet C et al (2011) New materials and devices for preventing catheter-related infections. *Ann Intensive Care* 1(1):34. https://doi.org/10.1186/2110-5820-1-34
32. Kleinschmidt S, Huygens F, Faoagali J et al (2015) *Staphylococcus epidermidis* as a cause of bacteremia. *Future Microbiol* 10(11): 1859–1879. https://doi.org/10.2217/fmb.15.98
33. Otto M (2009) *Staphylococcus epidermidis*: the 'accidental' pathogen. *Nat Rev Microbiol* 7(8):555–567. https://doi.org/10.1038/nrmicro2182
34. Hajipour MJ, Fromm KM, Akbar Ashkarran A et al (2012) Antibacterial properties of nanoparticles. *Trends Biotechnol* 30(10): 499–511. https://doi.org/10.1016/j.tibtech.2012.06.004
35. Ruhal R, Kataria R (2021) Biofilm patterns in gram-positive and gram-negative bacteria. *Microbiol Res* 251:126829. https://doi.org/10.1016/j.micres.2021.126829
36. Slavin YN, Asnis J, Häfeli UO et al (2017) Metal nanoparticles: understanding the mechanisms behind antibacterial activity. *J Nanobiotechnol* 15(1):65. https://doi.org/10.1186/s12951-017-0308-z
37. Reta A, Bitew Kifilie A, Mengist A (2019) Bacterial infections and their antibiotic resistance pattern in Ethiopia: a systematic review. *Adv Prev Med* 2019:4380309. https://doi.org/10.1155/2019/4380309
38. Schubeis T, Spehr J, Viereck J et al (2018) Structural and functional characterization of the Curli adaptor protein CsgF. *FEBS Lett* 592(6):1020–1029. https://doi.org/10.1002/1873-3468.13002
39. Tuson HH, Weibel DB (2013) Bacteria-surface interactions. *Soft Matter* 9(18):4368–4380. https://doi.org/10.1039/C3SM27705D
40. Zheng S, Bawazir M, Dhall A et al (2021) Implication of surface properties, bacterial motility, and hydrodynamic conditions on bacterial surface sensing and their initial adhesion. *Front Bioeng Biotechnol* 9:643722. https://doi.org/10.3389/fbioe.2021.643722
41. Oh JK, Yegin Y, Yang F et al (2018) The influence of surface chemistry on the kinetics and thermodynamics of bacterial adhesion. *Sci Rep* 8:17247. https://doi.org/10.1038/s41598-018-35343-1
42. Chen SF, Li LY, Zhao C et al (2010) Surface hydration: principles and applications toward low-fouling/nonfouling biomaterials. *Polymer* 51(23):5283–5293. https://doi.org/10.1016/j.polymer.2010.08.022
43. Mu MC, Liu SH, DeFlorio W et al (2023) Influence of surface roughness, nanostructure, and wetting on bacterial adhesion. *Langmuir* 39(15):5426–5439. https://doi.org/10.1021/acs.langmuir.3c00091
44. Chen YX, Ao J, Zhang JT et al (2023) Bioinspired superhydrophobic surfaces, inhibiting or promoting microbial contamination? *Mater Today* 67:468–494. https://doi.org/10.1016/j.mattod.2023.06.006
45. Mishra A, Aggarwal A, Khan F (2024) Medical device-associated infections caused by biofilm-forming microbial pathogens and controlling strategies. *Antibiotics* 13(7):623. https://doi.org/10.3390/antibiotics13070623
46. Grenho L, Manso MC, Monteiro FJ et al (2012) Adhesion of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* onto nanohydroxyapatite as a bone regeneration material. *J Biomed Mater Res Part A* 100A(7): 1823–1830. https://doi.org/10.1002/jbm.a.34139
47. Villani M, Consonni R, Canetti M et al (2020) Polyurethane-based composites: effects of antibacterial fillers on the physical-mechanical behavior of thermoplastic polyurethanes. *Polymers* 12(2):362. https://doi.org/10.3390/polym12020362
48. Bruenke J, Roschke I, Agarwal S et al (2016) Quantitative comparison of the antimicrobial efficiency of leaching versus non-leaching polymer materials. *Macromol Biosci* 16(5):647–654. https://doi.org/10.1002/mabi.201500266
49. CDC (Centers for Disease Control and Prevention) (2017) Updated Recommendations on the Use of Chlorhexidine-Impregnated Dressings for Prevention of Intravascular Catheter-Related Infections. https://www.cdc.gov/infection-control/hcp/c-i-dressings/index.html [Accessed on 30 October 2024]
50. Sousa C, Henriques M, Oliveira R (2011) Mini-review: antimicrobial central venous catheters – recent advances and strategies. *Biofouling* 27(6):609–620. https://doi.org/10.1080/08927014.2011.593261
51. Norris LB, Kablaoui F, Brilhart MK et al (2017) Systematic review of antimicrobial lock therapy for prevention of central-line-associated bloodstream infections in adult and pediatric cancer patients. *Int J Antimicrob Agents* 50(3):308–317. https://doi.org/10.1016/j.ijantimicag.2017.06.013
52. Zander ZK, Becker ML (2018) Antimicrobial and antifouling strategies for polymeric medical devices. *ACS Macro Lett* 7(1): 16–25. https://doi.org/10.1021/acsmacrolett.7b00879
53. Faustino CMC, Lemos SMC, Monge N et al (2020) A scope at antifouling strategies to prevent catheter-associated infections. *Adv Colloid Interface Sci* 284:102230. https://doi.org/10.1016/j.cis.2020.102230
54. Neoh KG, Li M, Kang ET et al (2017) Surface modification strategies for combating catheter-related complications: recent

advances and challenges. *J Mater Chem B* 5(11):2045–2067. https://doi.org/10.1039/C6TB03280J
55. Yeh SB, Chen CS, Chen WY et al (2014) Modification of silicone elastomer with zwitterionic silane for durable antifouling properties. *Langmuir* 30(38):11386–11393. https://doi.org/10.1021/la502486e
56. Ke Y, Meng HT, Du ZY et al (2024) Bioinspired superhydrophilic zwitterionic polymer armor combats thrombosis and infection of vascular catheters. *Bioact Mater* 37:493–504. https://doi.org/10.1016/j.bioactmat.2024.04.002
57. Leng C, Sun SW, Zhang KX et al (2016) Molecular level studies on interfacial hydration of zwitterionic and other antifouling polymers in situ. *Acta Biomater* 40:6–15. https://doi.org/10.1016/j.actbio.2016.02.030
58. Wang XW, Wang J, Yu Y et al (2022) A polyzwitterion-based antifouling and flexible bilayer hydrogel coating. *Compos Part B Eng* 244:110164. https://doi.org/10.1016/j.compositesb.2022.110164
59. Francolini I, Silvestro I, Di Lisio V et al (2019) Synthesis, characterization, and bacterial fouling-resistance properties of polyethylene glycol-grafted polyurethane elastomers. *Int J Mol Sci* 20(4):1001. https://doi.org/10.3390/ijms20041001
60. Malhotra A, Chauhan SR, Rahaman M et al (2023) Phyto-assisted synthesis of zinc oxide nanoparticles for developing antibiofilm surface coatings on central venous catheters. *Front Chem* 11:1138333. https://doi.org/10.3389/fchem.2023.1138333
61. Wallace A, Albadawi H, Patel N et al (2017) Anti-fouling strategies for central venous catheters. *Cardiovasc Diagn Ther* 7(S3): S246–S257. https://doi.org/10.21037/cdt.2017.09.18
62. Ribeiro M, Monteiro FJ, Ferraz MP (2012) *Staphylococcus aureus* and *Staphylococcus epidermidis* adhesion to nanohydroxyapatite in the presence of model proteins. *Biomed Mater* 7(4):045010. https://doi.org/10.1088/1748-6041/7/4/045010
63. Mathew E, Domínguez-Robles J, Stewart SA et al (2019) Fused deposition modeling as an effective tool for anti-infective dialysis catheter fabrication. *ACS Biomater Sci Eng* 5(11):6300–6310. https://doi.org/10.1021/acsbiomaterials.9b01185
64. Zhang HB, Mu CA (2015) Anti-fouling coatings of poly(dimethylsiloxane) devices for biological and biomedical applications. *J Med Biol Eng* 35(2):143–155. https://doi.org/10.1007/s40846-015-0029-4
65. May RM, Magin CM, Mann EE et al (2015) An engineered micropattern to reduce bacterial colonization, platelet adhesion and fibrin sheath formation for improved biocompatibility of central venous catheters. *Clin Transl Med* 4(1):e9. https://doi.org/10.1186/s40169-015-0050-9
66. Maikranz E, Spengler C, Thewes N et al (2020) Different binding mechanisms of *Staphylococcus aureus* to hydrophobic and hydrophilic surfaces. *Nanoscale* 12(37):19267–19275. https://doi.org/10.1039/d0nr03134h
67. Borges I, Henriques PC, Gomes RN et al (2020) Exposure of smaller and oxidized graphene on polyurethane surface improves its antimicrobial performance. *Nanomaterials* 10(2):349. https://doi.org/10.3390/nano10020349
68. Gomes RN, Borges I, Pereira AT et al (2018) Antimicrobial graphene nanoplatelets coatings for silicone catheters. *Carbon* 139: 635–647. https://doi.org/10.1016/j.carbon.2018.06.044
69. Zander ZK, Chen PR, Hsu YH et al (2018) Post-fabrication QAC-functionalized thermoplastic polyurethane for contact-killing catheter applications. *Biomaterials* 178:339–350. https://doi.org/10.1016/j.biomaterials.2018.05.010
70. Ricardo SIC, Anjos IIL, Monge N et al (2020) A glance at antimicrobial strategies to prevent catheter-associated medical infections. *ACS Infect Dis* 6(12):3109–3130. https://doi.org/10.1021/acsinfecdis.0c00526
71. Liu YM, Wen J, Gao Y et al (2018) Antibacterial graphene oxide coatings on polymer substrate. *Appl Surf Sci* 436: 624–630. https://doi.org/10.1016/j.apsusc.2017.12.006
72. Ribeiro KL, Frías IAM, Franco OL et al (2018) Clavanin A-bioconjugated Fe_3O_4/Silane core-shell nanoparticles for thermal ablation of bacterial biofilms. *Colloids Surf B Biointerfaces* 169: 72–81. https://doi.org/10.1016/j.colsurfb.2018.04.055
73. Krikava I, Kolar M, Garajova B et al (2020) The efficacy of a non-leaching antibacterial central venous catheter - a prospective, randomized, double-blind study. *Biomed Pap Olomouc* 164(2):154–160. https://doi.org/10.5507/bp.2019.022
74. Vazquez-Rodriguez JA, Shaqour B, Guarch-Pérez C et al (2022) A Niclosamide-releasing hot-melt extruded catheter prevents *Staphylococcus aureus* experimental biomaterial-associated infection. *Sci Rep* 12:12329. https://doi.org/10.1038/s41598-022-16107-4
75. Neethu S, Midhun SJ, Radhakrishnan EK et al (2020) Surface functionalization of central venous catheter with mycofabricated silver nanoparticles and its antibiofilm activity on multidrug resistant *Acinetobacter baumannii*. *Microb Pathog* 138:103832. https://doi.org/10.1016/j.micpath.2019.103832
76. Wu K, Yang Y, Zhang YM et al (2015) Antimicrobial activity and cytocompatibility of silver nanoparticles coated catheters via a biomimetic surface functionalization strategy. *Int J Nanomed* 10:7241–7252. https://doi.org/10.2147/IJN.S92307
77. Lungren MP, Donlan RM, Kankotia R et al (2014) Bacteriophage K antimicrobial-lock technique for treatment of *Staphylococcus aureus* central venous catheter–related infection: a leporine model efficacy analysis. *J Vasc Interv Radiol* 25(10): 1627–1632. https://doi.org/10.1016/j.jvir.2014.06.009
78. Lungren MP, Christensen D, Kankotia R et al (2013) Bacteriophage K for reduction of *Staphylococcus aureus* biofilm on central venous catheter material. *Bacteriophage* 3(4):e26825. https://doi.org/10.4161/bact.26825
79. Raman N, Marchillo K, Lee MR et al (2016) Intraluminal release of an antifungal β-peptide enhances the antifungal and anti-biofilm activities of multilayer-coated catheters in a rat model of venous catheter infection. *ACS Biomater Sci Eng* 2(1): 112–121. https://doi.org/10.1021/acsbiomaterials.5b00427
80. Applerot G, Lipovsky A, Dror R et al (2009) Enhanced antibacterial activity of nanocrystalline ZnO due to increased ROS-mediated cell injury. *Adv Funct Mater* 19(6):842–852. https://doi.org/10.1002/adfm.200801081
81. Teleflex (2015) Chlorag^{+}ard® Technology Information. https://teleflexvascular.com/files/ifu/A-41000-103A.pdf [Accessed on 30 September 2024]
82. Teleflex (2022) Short-Term Central Venous Catheters (CVC) | Arrowg+ard Blue Plus® CVC. https://www.teleflex.com/usa/en/product-areas/vascular-access/central-access/short-term-cvc/ [Accessed on 30 September 2024]
83. Teleflex (2018) Arrowg+ard Blue Protection Clinical References. https://www.teleflex.com/usa/en/product-areas/vascular-access/central-access/short-term-cvc/Arrowgard-Blue-Plus-Clinical-Reference-MC-004391Rev1.pdf [Accessed on 30 September 2024]

84. Lorente L, Lecuona M, Jiménez A et al (2016) Chlorhexidine-silver sulfadiazine-impregnated venous catheters are efficient even at subclavian sites without tracheostomy. *Am J Infect Control* 44(12):1526–1529. https://doi.org/10.1016/j.ajic.2016.04.236
85. Cook Medical (2012) Cook Spectrum® Central Venous Catheter Set and Tray. https://www.cookmedical.com/products/12eee5a3-ccf0-476c-a180-054be6accdd0/ [Accessed on 30 September 2024]
86. Medline (2025) Vantex® Antimicrobial Central Venous Catheter. https://www.medline.com/infection-prevention/antimicrobialcentral-venous-catheter/ [Accessed on 30 November 2024]
87. Ranucci M, Isgrò G, Giomarelli PP et al (2003) Impact of oligon central venous catheters on catheter colonization and catheter-related bloodstream infection. *Crit Care Med* 31(1): 52–59. https://doi.org/10.1097/00003246-200301000-00008
88. LoVetri K, Gawande PV, Yakandawala N et al (2010) Biofouling and anti-fouling of medical devices. In: Chan J, Wong S (Eds.), Biofouling: Types, Impact and Anti-Fouling. Nova Science Publishers, p.105–127
89. Vygon (2024) Antimicrobial Multi-lumen CVC-Expert | Multicath 3 Expert. https://www.vygon.com/en/products/vascular/adult-central-venous-catheters-cvc/antimicrobial-multilumen-cvc-expert/multicath-3-expert [Accessed on 30 September 2024]
90. Loertzer H, Soukup J, Hamza A et al (2006) Use of catheters with the AgION antimicrobial system in kidney transplant recipients to reduce infection risk. *Transplant Proc* 38(3):707–710. https://doi.org/10.1016/j.transproceed.2006.01.064
91. Vygon (2024) Antimicrobial Multi-lumen CVC - STAR | Multistar 3 UP. https://www.vygon.com/en/products/vascular/adult-central-venous-catheters-cvc/antimicrobial-multi-lumen-cvc-star/multistar-3 [Accessed on 30 September 2024]
92. Greenhalgh R, Dempsey-Hibbert NC, Whitehead KA (2019) Antimicrobial strategies to reduce polymer biomaterial infections and their economic implications and considerations. *Int Biodeterior Biodegrad* 136:1–14. https://doi.org/10.1016/j.ibiod.2018.10.005
93. Lepu Medical (2024) Safecath Plus Antimicrobial Central Venous Catheter. https://en.lepumedical.com/productinfo421.html [Accessed on 30 November 2025]
94. B | Braun (2020) Certofix® Protect. https://www.bbraun.com/en/products-and-solutions/therapies/vascular-access/central-venous-catheter-certofix-.html#certofix-protect [Accessed on 30 September 2024]
95. Kimal (2016) Altius® ProActiv+™. https://www.ssemmthembu.co.za/images/PDFs/Kimal/L-0155-0113-A1__KIMAL_ALTIUS_PROACTIVE_A4_2PP_LEAFLET_03-16_AW.PDF [Accessed on 30 October 2024]
96. Bactiguard (2025) BIP Central Venous Catheter. https://www.bactiguard.com/medical-devices/intensive-care/bip-central-venous-catheter/ [Accessed on 30 November 2025]
97. Asadi A, Abdi M, Kouhsari E et al (2020) Minocycline, focus on mechanisms of resistance, antibacterial activity, and clinical effectiveness: back to the future. *J Glob Antimicrob Resist* 22: 161–174. https://doi.org/10.1016/j.jgar.2020.01.022
98. Campbell EA, Korzheva N, Mustaev A et al (2001) Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. *Cell* 104(6):901–912. https://doi.org/10.1016/S0092-8674(01)00286-0
99. Viola GM, Rosenblatt J, Raad II (2017) Drug eluting antimicrobial vascular catheters: progress and promise. *Adv Drug Deliv Rev* 112:35–47. https://doi.org/10.1016/j.addr.2016.07.011
100. Sowlati-Hashjin S, Carbone P, Karttunen M (2020) Insights into the polyhexamethylene biguanide (PHMB) mechanism of action on bacterial membrane and DNA: a molecular dynamics study. *J Phys Chem B* 124(22):4487–4497. https://doi.org/10.1021/acs.jpcb.0c02609
101. Li BY, Webster TJ (2018) Bacteria antibiotic resistance: new challenges and opportunities for implant-associated orthopedic infections. *J Orthop Res* 36(1):22–32. https://doi.org/10.1002/jor.23656
102. Murray CJL, Ikuta KS, Sharara F et al (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 399(10325):629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
103. Tang ZX, Lv BF (2014) MgO nanoparticles as antibacterial agent: preparation and activity. *Braz J Chem Eng* 31(3): 591–601. https://doi.org/10.1590/0104-6632.20140313s00002813
104. Li Y, Zhang W, Niu JF et al (2012) Mechanism of photogenerated reactive oxygen species and correlation with the antibacterial properties of engineered metal-oxide nanoparticles. *ACS Nano* 6(6):5164–5173. https://doi.org/10.1021/nn300934k
105. European Commission (2022) Commission Recommendation of 10 June 2022 on the Definition of Nanomaterial (Text with EEA Relevance) 2022/C 229/01. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022H0614(01) [Accessed on 30 September 2024]
106. Modena MM, Rühle B, Burg TP et al (2019) Nanoparticle characterization: what to measure? *Adv Mater* 31(32):1901556. https://doi.org/10.1002/adma.201901556
107. Besinis A, De Peralta T, Handy RD (2014) The antibacterial effects of silver, titanium dioxide and silica dioxide nanoparticles compared to the dental disinfectant chlorhexidine on *Streptococcus mutans* using a suite of bioassays. *Nanotoxicology* 8(1):1–16. https://doi.org/10.3109/17435390.2012.742935
108. Nguyen NT, Grelling N, Wetteland CL et al (2018) Antimicrobial activities and mechanisms of magnesium oxide nanoparticles (nMgO) against pathogenic bacteria, yeasts, and biofilms. *Sci Rep* 8:16260. https://doi.org/10.1038/s41598-018-34567-5
109. Choi O, Hu ZQ (2008) Size dependent and reactive oxygen species related nanosilver toxicity to nitrifying bacteria. *Environ Sci Technol* 42(12):4583–4588. https://doi.org/10.1021/es703238h
110. Long TC, Saleh N, Tilton RD et al (2006) Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): implications for nanoparticle neurotoxicity. *Environ Sci Technol* 40(14):4346–4352. https://doi.org/10.1021/es060589n
111. Cotton GC, Lagesse NR, Parke LS et al (2019) Antibacterial nanoparticles. In: Andrews DL, Lipson RH, Nann T (Eds.), Comprehensive Nanoscience and Nanotechnology (2nd Ed.). Elsevier, p.65–82. https://doi.org/10.1016/B978-0-12-803581-8.10409-6
112. Sawai J (2003) Quantitative evaluation of antibacterial activities of metallic oxide powders (ZnO, MgO and CaO) by conductimetric assay. *J Microbiol Meth* 54(2):177–182. https://doi.org/10.1016/S0167-7012(03)00037-X
113. Krishnamoorthy K, Manivannan G, Kim SJ et al (2012) Antibacterial activity of MgO nanoparticles based on lipid peroxidation by oxygen vacancy. *J Nanopart Res* 14(9):1063. https://doi.org/10.1007/s11051-012-1063-6

114. Krishnamoorthy K, Moon JY, Hyun HB et al (2012) Mechanistic investigation on the toxicity of MgO nanoparticles toward cancer cells. *J Mater Chem* 22(47):24610–24617. https://doi.org/10.1039/C2JM35087D
115. Das B, Moumita S, Ghosh S et al (2018) Biosynthesis of magnesium oxide (MgO) nanoflakes by using leaf extract of *Bauhinia purpurea* and evaluation of its antibacterial property against *Staphylococcus aureus*. *Mater Sci Eng C Mater Biol Appl* 91: 436–444. https://doi.org/10.1016/j.msec.2018.05.059
116. More PR, Pandit S, De Filippis A et al (2023) Silver nanoparticles: bactericidal and mechanistic approach against drug resistant pathogens. *Microorganisms* 11(2):369. https://doi.org/10.3390/microorganisms11020369
117. Pasquet J, Chevalier Y, Pelletier J et al (2014) The contribution of zinc ions to the antimicrobial activity of zinc oxide. *Colloids Surf A Physicochem Eng Aspects* 457:263–274. https://doi.org/10.1016/j.colsurfa.2014.05.057
118. Horie M, Fujita K, Kato H et al (2012) Association of the physical and chemical properties and the cytotoxicity of metal oxide nanoparticles: metal ion release, adsorption ability and specific surface area. *Metallomics* 4(4):350–360. https://doi.org/10.1039/C2MT20016C
119. Stanić V, Dimitrijević S, Antić-Stanković J et al (2010) Synthesis, characterization and antimicrobial activity of copper and zinc-doped hydroxyapatite nanopowders. *Appl Surf Sci* 256(20): 6083–6089. https://doi.org/10.1016/j.apsusc.2010.03.124
120. Perelshtein I, Applerot G, Perkas N et al (2010) Ultrasound radiation as a "throwing stones" technique for the production of antibacterial nanocomposite textiles. *ACS Appl Mater Interfaces* 2(7):1999–2004. https://doi.org/10.1021/am100291w
121. Dimapilis EAS, Hsu CS, Mendoza RMO et al (2018) Zinc oxide nanoparticles for water disinfection. *Sustain Environ Res* 28(2):47–56. https://doi.org/10.1016/j.serj.2017.10.001
122. Ivask A, Kurvet I, Kasemets K et al (2014) Size-dependent toxicity of silver nanoparticles to bacteria, yeast, algae, crustaceans and mammalian cells in vitro. *PLoS ONE* 9(7):e102108. https://doi.org/10.1371/journal.pone.0102108
123. Grenho L, Jorge Monteiro F, Pia Ferraz M (2014) In vitro analysis of the antibacterial effect of nanohydroxyapatite–ZnO composites. *J Biomed Mater Res Part A* 102(10):3726–3733. https://doi.org/10.1002/jbm.a.35042
124. Leung YH, Ng AMC, Xu XY et al (2014) Mechanisms of antibacterial activity of MgO: non-ROS mediated toxicity of MgO nanoparticles towards *Escherichia coli*. *Small* 10(6):1171–1183. https://doi.org/10.1002/smll.201302434
125. Li YQ, Yang D, Wang S et al (2018) The detailed bactericidal process of ferric oxide nanoparticles on *E. coli*. *Molecules* 23(3): 606. https://doi.org/10.3390/molecules23030606
126. Pang H, Gao F, Lu QY (2009) Morphology effect on antibacterial activity of cuprous oxide. *Chem Commun* (9):1076–1078. https://doi.org/10.1039/B816670F
127. Wang X, Wu HF, Kuang Q et al (2010) Shape-dependent antibacterial activities of Ag_2O polyhedral particles. *Langmuir* 26(4):2774–2778. https://doi.org/10.1021/la9028172
128. Azam A, Ahmed AS, Oves M et al (2012) Antimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria: a comparative study. *Int J Nanomed* 7: 6003–6009. https://doi.org/10.2147/IJN.S35347
129. Ahamed M, Alhadlaq HA, Majeed Khan MA et al (2014) Synthesis, characterization, and antimicrobial activity of copper oxide nanoparticles. *J Nanomater* 2014:637858. https://doi.org/10.1155/2014/637858
130. Albers CE, Hofstetter W, Siebenrock KA et al (2013) In vitro cytotoxicity of silver nanoparticles on osteoblasts and osteoclasts at antibacterial concentrations. *Nanotoxicology* 7(1):30–36. https://doi.org/10.3109/17435390.2011.626538
131. Franco D, Calabrese G, Guglielmino SPP et al (2022) Metal-based nanoparticles: antibacterial mechanisms and biomedical application. *Microorganisms* 10(9):1778. https://doi.org/10.3390/microorganisms10091778
132. Mijnendonckx K, Leys N, Mahillon J et al (2013) Antimicrobial silver: uses, toxicity and potential for resistance. *Biometals* 26(4):609–621. https://doi.org/10.1007/s10534-013-9645-z
133. Beyth N, Houri-Haddad Y, Domb A et al (2015) Alternative antimicrobial approach: nano-antimicrobial materials. *Evid Based Complementary Altern Med* 2015:246012. https://doi.org/10.1155/2015/246012
134. Szycher M (1991) High Performance Biomaterials: a Comprehensive Guide to Medical and Pharmaceutical Applications (1st Ed.). Routledge. https://doi.org/10.1201/9780203752029
135. Wagner WR, Sakiyama-Elbert SE, Zhang GG et al (2020) Biomaterials Science: an Introduction to Materials in Medicine (4th Ed.). Elsevier. https://doi.org/10.1016/C2017-0-02323-6
136. McKeen L (2018) Styrenic plastics. In: The Effect of Sterilization Methods on Plastics and Elastomers (4th Ed.). Elsevier, p.91–138. https://doi.org/10.1016/b978-0-12-814511-1.00004-4
137. Backes EH, Harb SV, Pinto LA et al (2024) Thermoplastic polyurethanes: synthesis, fabrication techniques, blends, composites, and applications. *J Mater Sci* 59(4):1123–1152. https://doi.org/10.1007/s10853-023-09077-z
138. Alves P, Ferreira P, Gil H (2012) Biomedical polyurethane-based materials. In: Cavaco LI, Melo JA (Eds.), Polyurethane: Properties, Structure and Applications. Nova Science Publishers, Incorporated, New York, p.25–50
139. Thomas S, Datta J, Haponiuk JT et al (2017) Polyurethane Polymers: Composites and Nanocomposites (1st Ed.). Elsevier
140. Mauro M (2002) Central Venous Catheters: Materials, Design and Selection, in Venous Catheters: a Practical Manual. Thieme, New York, p.76–84
141. Kiran S, James NR, Jayakrishnan A et al (2012) Polyurethane thermoplastic elastomers with inherent radiopacity for biomedical applications. *J Biomed Mater Res* 100A(12):3472–3479. https://doi.org/10.1002/jbm.a.34295
142. Harper CA (2000) Modern Plastics Handbook. McGraw-Hill Education
143. Olmos D, González-Benito J (2021) Polymeric materials with antibacterial activity: a review. *Polymers* 13(4):613. https://doi.org/10.3390/polym13040613
144. Singh J, Singh K, Saini J et al (2018) Processing of polymers and their composites: a review. *Encycl Mater Compos* 1(2018): 577–603. https://doi.org/10.1016/B978-0-12-803581-8.11435-3
145. Wentling AG (2004) Hemodialysis catheters: materials, design and manufacturing. *Contrib Nephrol* 142:112–127. https://doi.org/10.1159/000074869
146. Mathew E, Domínguez-Robles J, Larrañeta E et al (2019) Fused deposition modelling as a potential tool for antimicrobial dialysis catheters manufacturing: new trends vs. conventional approaches. *Coatings* 9(8):515.

https://doi.org/10.3390/coatings9080515
147. Lubrizol (2024) Precision Medical Extrusion of Thermoplastics and Silicone. https://media.lubrizol.com/-/media/Project/Lubrizol-Corporation/Lubrizol/Master-Site/Health/Documents/Literature/Precision-Medical-Extrusion-of-Thermoplastics-and-Silicone.pdf [Accessed on 30 November 2024]
148. Kum CH, Cho Y, Seo SH et al (2014) A poly(lactide) stereo complex structure with modified magnesium oxide and its effects in enhancing the mechanical properties and suppressing inflammation. *Small* 10(18):3783–3794. https://doi.org/10.1002/smll.201302880
149. Hickey DJ, Ercan B, Sun LL et al (2015) Adding MgO nanoparticles to hydroxyapatite-PLLA nanocomposites for improved bone tissue engineering applications. *Acta Biomater* 14:175–184. https://doi.org/10.1016/j.actbio.2014.12.004
150. Aničić N, Kurtjak M, Jeverica S et al (2021) Antimicrobial polymeric composites with embedded nanotextured magnesium oxide. *Polymers* 13(13):2183. https://doi.org/10.3390/polym13132183
151. Kravanja KA, Finšgar M (2022) A review of techniques for the application of bioactive coatings on metal-based implants to achieve controlled release of active ingredients. *Mater Des* 217: 110653. https://doi.org/10.1016/j.matdes.2022.110653
152. Neacşu IA, Nicoară AI, Vasile OR et al (2016) Inorganic micro- and nanostructured implants for tissue engineering. In: Grumezescu AM (Ed.), Nanobiomaterials in Hard Tissue Engineering. Elsevier, p.271–295. https://doi.org/10.1016/b978-0-323-42862-0.00009-2
153. Thomas R, Mathew S, Nayana AR et al (2017) Microbially and phytofabricated AgNPs with different mode of bactericidal action were identified to have comparable potential for surface fabrication of central venous catheters to combat *Staphylococcus aureus* biofilm. *J Photochem Photobiol B Biol* 171:96–103. https://doi.org/10.1016/j.jphotobiol.2017.04.036
154. Stevens KNJ, Crespo-Biel O, van den Bosch EEM et al (2009) The relationship between the antimicrobial effect of catheter coatings containing silver nanoparticles and the coagulation of contacting blood. *Biomaterials* 30(22):3682–3690. https://doi.org/10.1016/j.biomaterials.2009.03.054
155. Stevens KNJ, Croes S, Boersma RS et al (2011) Hydrophilic surface coatings with embedded biocidal silver nanoparticles and sodium heparin for central venous catheters. *Biomaterials* 32(5):1264–1269. https://doi.org/10.1016/j.biomaterials.2010.10.042
156. Vafa Homann M, Johansson D, Wallen H et al (2016) Improved ex vivo blood compatibility of central venous catheter with noble metal alloy coating. *J Biomed Mater Res* 104(7):1359–1365. https://doi.org/10.1002/jbm.b.33403
157. Jamal MA, Hachem RY, Rosenblatt J et al (2015) *In vivo* biocompatibility and *in vitro* efficacy of antimicrobial gendine-coated central catheters. *Antimicrob Agents Chemother* 59(9):5611–5618. https://doi.org/10.1128/aac.00834-15
158. Raad I, Mohamed JA, Reitzel RA et al (2012) Improved antibiotic-impregnated catheters with extended-spectrum activity against resistant bacteria and fungi. *Antimicrob Agents Chemother* 56(2):935–941. https://doi.org/10.1128/aac.05836-11
159. Jamal MA, Rosenblatt J, Jiang Y et al (2014) Prevention of transmission of multidrug-resistant organisms during catheter exchange using antimicrobial catheters. *Antimicrob Agents Chemother* 58(9):5291–5296. https://doi.org/10.1128/AAC.02886-14
160. Jamal MA, Rosenblatt JS, Hachem RY et al (2014) Prevention of biofilm colonization by Gram-negative bacteria on minocycline-rifampin-impregnated catheters sequentially coated with chlorhexidine. *Antimicrob Agents Chemother* 58(2):1179–1182. https://doi.org/10.1128/AAC.01959-13
161. Mendoza G, Regiel-Futyra A, Tamayo A et al (2018) Chitosan-based coatings in the prevention of intravascular catheter-associated infections. *J Biomater Appl* 32(6):725–737. https://doi.org/10.1177/0885328217739199
162. Liu L, Yu H, Wang L et al (2024) Heparin-network-mediated long-lasting coatings on intravascular catheters for adaptive antithrombosis and antibacterial infection. *Nat Commun* 15(1): 107. https://doi.org/10.1038/s41467-023-44478-3
163. Ferreira CAM, Guerreiro SFC, Padrão T et al (2024) Antimicrobial nanofibers to fight multidrug-resistant bacteria. In: Wani MY, Wani IA, Rai A (Eds.), Nanotechnology Based Strategies for Combating Antimicrobial Resistance. Springer Nature Singapore, p.533–579. https://doi.org/10.1007/978-981-97-2023-1_20
164. Angel N, Li SN, Yan F et al (2022) Recent advances in electrospinning of nanofibers from bio-based carbohydrate polymers and their applications. *Trends Food Sci Technol* 120:308–324. https://doi.org/10.1016/j.tifs.2022.01.003
165. Lee JC, In SH, Lee JH et al (2023) Electrospun polycaprolactone/polyvinylidene fluoride composite nanofibers for fabricating artificial conduits for ureteral stricture treatment. *ACS Appl Nano Mater* 6(24):22757–22766. https://doi.org/10.1021/acsanm.3c03716
166. Xu HF, Xu H, Ma SL et al (2023) Bifunctional electrospun poly (L-lactic acid) membranes incorporating black phosphorus nanosheets and nano-zinc oxide for enhanced biocompatibility and antibacterial properties in catheter materials. *J Mech Behav Biomed Mater* 142:105884. https://doi.org/10.1016/j.jmbbm.2023.105884
167. Suresh S, Black RA (2015) Electrospun polyurethane as an alternative ventricular catheter and in vitro model of shunt obstruction. *J Biomater Appl* 29(7):1028–1038. https://doi.org/10.1177/0885328214551587
168. Wang D, Dong RH, Wang XD et al (2022) Flexible electronic catheter based on nanofibers for the *in vivo* elimination of circulating tumor cells. *ACS Nano* 16(4):5274–5283. https://doi.org/10.1021/acsnano.1c09807
169. Levana O, Hong S, Kim SH et al (2022) A novel strategy for creating an antibacterial surface using a highly efficient electrospray-based method for silica deposition. *Int J Mol Sci* 23(1):513. https://doi.org/10.3390/ijms23010513
170. Weisman JA, Ballard DH, Jammalamadaka U et al (2019) 3D printed antibiotic and chemotherapeutic eluting catheters for potential use in interventional radiology in vitro proof of concept study. *Acad Radiol* 26(2):270–274. https://doi.org/10.1016/j.acra.2018.03.022
171. Ng WL, An J, Chua CK (2024) Process, material, and regulatory considerations for 3D printed medical devices and tissue constructs. *Engineering* 36:146–166. https://doi.org/10.1016/j.eng.2024.01.028