REVIEW ARTICLE

Drug-Coated Central Venous Catheters - A Comprehensive Review of Strategies in the Development to Overcome Biofilm Formation and Related Infections

Nissara Ahammed[1*], Revathi Sundaramoorthi[2], Venkatesh Dinnekere Puttegowda[3]

[1]*Department of Pharmaceutics, School of Pharmacy, Sri Balaji Vidyapeeth Deemed to be University, Pillaiyarkuppam, Puducherry, India.*

[2]*Department of Pharmaceutics, School of Pharmacy, Sri Balaji Vidyapeeth Deemed to be University, Pillaiyarkuppam, Puducherry, India.*

[3]*Department of Pharmaceutics, Acharya B.M. Reddy college of Pharmacy, Bengaluru, India*

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ABSTRACT

Central venous catheters (CVCs) are implantable medical instruments regularly used in intense care units for the easy introduction of medical drugs and medicaments, to give fluids intravenously, nutriments, transfusion of blood and also to withdraw blood samples. Bloodstream infections associated with the usage of catheters are the most recurrent, harmful as well as expensive impediment. This is the omnipresent reason for the introduction of bacteria and related infections. Among the various types of medical devices, the rate of infection, morbidity and mortality are higher with the usage of CVCs than any other types of medical instruments. Biofilm developed due to contamination by microorganisms. The biofilm is a bunch of microorganisms accumulated on the surface of CVCs. These biofilms contribute to the proliferation of microbes and increase antimicrobial resistance against antibiotics, affect the host's immunity and get spread to the various body parts. Numerous approaches have been evolved to overcome the above mentioned issues associated with the usage of CVCs. In the said review, the authors have summarized the usage of CVCs, biofilm formation, development of infection, strategies and innovations in the modification of CVCs aiming to avoid the CRBSI and subsequent resistance to antimicrobial drugs.

Keywords: Drug-coated central venous catheters, Biofilm, Catheter-related bloodstream infections, Resistance, Coated catheters.

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INTRODUCTION

Central venous catheter (CVC) (Figure 1) is a category of medical instrument, which has a hollow bendable tube. It is inserted into a large, central vein like an internal jugular, subclavian, or femoral vein and advanced until the terminal lumen resides within the inferior vena cava, superior vena cava, or right atrium.[1] The process of central venous catheterization was introduced in 1929 by Dr. Werner Forssmann and this technique further advanced and became vital for the treatment of patients at intensive care units (ICU).[2] Catheter-related bloodstream infections (CRBSI) are the greatest persistent, dangerous, and expensive impediment to the usage of CVC and also the ubiquitous reason for healthcare-associated bacteremia. Among the various types of medical devices, the rate of infection, sickness and death are higher due to the usage of CVCs than any other types of medical instruments and also the main source of bacteremia and septicemia in ICU patients. The majority of infections of blood are associated with the improper usage of CVCs and using CVCs compared to peripheral venous catheters can escalate the relative risk of CRBSI by many folds.[3]

Biofilm formed on the surface of the CVC as a result of microbial contamination. Biofilm is a bunch of microorganisms that are hoarded and develop microbial conglomerates on the surface of CVC and get ingrained in an extracellular matrix. Because of these biofilms, the bacteria are able to survive against antimicrobial drugs in the human immune system and to spread to different parts of the body.[4] In order

*Author for Correspondence: nisarmpharm@gmail.com

to overcome CRBSI, various approaches have been evolved. The most researched among them is the innovation of CVCs, either coated or impregnated, with antimicrobial agents.[5] These catheters are believed to bring down the fatal events of CRBSIs by reducing the colonization of microbes on the catheter surfaces.[6] This article's main goal is to review and compute forms of CVC, insertion sites, complications, and various innovations to overcome the complications associated with the usage of CVC.

REVIEW

Central Venous Catheter

A CVC is a narrow, bendable, thin tube that is placed into a big vein close to the heart. It can also be introduced through a vein in the neck, chest, or arm, (i.e., central venous line or central line). Catheters have 1, 2, and 3 tubes and are designated as single-lumen, double lumen and triple-lumen catheters, respectively. With the help of CVC, multiple treatments can be given at once. The duration of implantation of catheters may be weeks, months, or years. Easy introduction of drugs and other medicines, giving intravenous fluids, nutrition, blood and blood products and also drawing of blood samples can be easily achieved with the aid of CVCs.[7]

Importance of Central Venous Catheter[8]

The major importance of a central line constitutes the following:

- Intravenous therapy requiring a longer duration of treatment, like antibiotics or chemotherapy, can be delivered for a longer duration of time due to the good tolerance of the catheter by the larger veins than smaller veins.
- Due to the lesser likelihood of CVC dislodgement, the intravenous medications can be delivered as an outpatient without hindering the patient's routine activity and these medicines can be received even at home.
- When a person is unconscious, the CVCs facilitate the delivery of large quantities of fluids or blood swiftly.
- The CVCs help in determining the quantity of fluid needed by a person by directly quantifying the arterial pressure in a central vein.
- The usage of CVC reduces the recurrent needle sticks and enables to take frequent blood samples without causing patient inconvenience.
- The nutrition can be directly delivered when a patient is unable to take them orally.
- Provides ease in patients with kidney failure as the hemodialysis machine that clears the body of waste and extra fluid can be connected directly to CVC.

Types of Central Venous Catheters

Tunneled catheters

These catheters are of choice when there is a necessity for central venous catheterization for more than two weeks to avoid frequent needle pricks and for the regular administration of medicaments, which cannot be administered through the regular intravenous lines. Administering chemotherapeutic drugs, nutrition and fluids and drawing blood samples can be achieved with this.

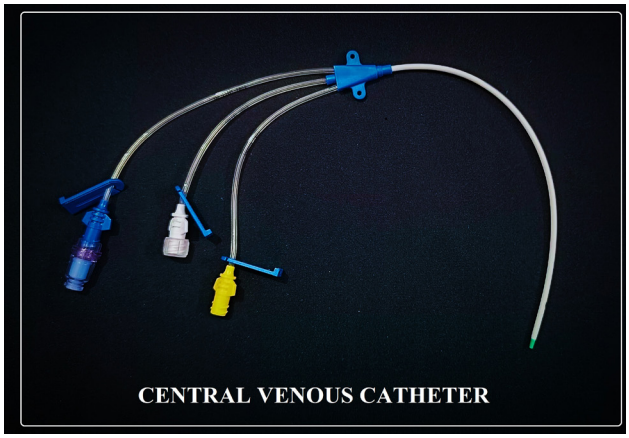

Figure 1: Central venous catheter [Triple lumen]

The tunneled catheters can be introduced through a vein in the neck and implanted it into the superior vena cava of heart with the help of ultrasound and live X-ray fluoroscopy. The one more end of the catheter is tunneled beneath the skin and passage out from the side of the chest.[9]

Non-tunneled catheters

These catheters are of choice when the venous access required is temporary or for a shorter duration of time and when faster administration of drugs or nutrition is desired. They are placed into big vein near the neck, chest or groin. They help in preventing catheter related thrombosis and thereby help in reducing the episodes of infection.[10]

Peripherally inserted catheters [PICC]

PICCs can be used when the peripheral sites of the body through the skin need to be accessed. They stretch out to the larger vein that supplies blood to the heart. They remain implanted in place for days or weeks.[11] They are useful for a variety of purposes in both in-patients and outpatients, primarily for the administration of intravenous antibiotics, parenteral nutrition plasmapheresis, apheresis, and chemotherapy.[12,13]

As with other CVCs, they can be single or multiple-lumen. Delivery of all medicines, infusates, and blood sampling can be achieved with PICCs. Insertion of PICCs may require local anesthesia in some patients.[14]

Totally implantable catheters

Totally implantable catheters are of choice when continuous venous access is not desired. The implantable catheters are implanted under the skin via a small slit and it consists of a reservoir that connects to the central circulation via a tunnel beneath the skin. A self-sealing septum and a chamber constitute a reservoir. With the help of a small Huber needle, venous access can be achieved percutaneously through the septum. Ports are either single-lumen or double-lumen.[15,16]

CVCs can be implanted through three main access sites: Internal jugular, femoral, and subclavian veins. The choice of

access site mainly depends on various parameters like clinical parameters, expertise of the clinician and preference.[17]

Because of its favorable anatomy, the convenience of access, low likelihood of problems, simplicity with the usage of ultrasound guidance, its wide surface area and superficiality the internal jugular vein is the preferred site for cannulation.[18 19] The infectious and thrombotic hitches are less with subclavian vein site.[20] A shorter distance from the lesion to the vein, a straighter and shorter distance to the lung and an optimal scenario for insertion at the clavisternomastoid angle are all provided by the supra-clavicular approach.[21]

Catheter-related bloodstream infections

CRBSI is the growth of biofilm caused by bacteria entering due to the usage of CVC. Biofilm formation and subsequent development of CRBSI is the utmost persistent, deadly and expensive impediments of using CVC that may lead to extended periods of hospitalisation. Among any other type of medical device, the greater risk of acquiring device-related illness and subsequent death is alarming by the use of catheters.[3] Intravascular devices and catheters of any kind carry a threat of infection, and CRBSI is now a common cause of fungemia and bacteremia.[22,23]

CRBSIs are a prominent infection in ICU patients. The sepsis developed can lead to multiple organ failure due to a hindered host immune response to an infection. Since several bacteria can induce catheter-related infections, this can lead to systemic inflammatory response syndrome and disrupt host homeostasis by stimulating the iron-sequestering ferritin H chain.[24] CRBSI activates a strong immune response, ranging from elevated body temperature, septic shock and damage of multiple organs. The stated mortality rate varies from 3 to 25%.[25]

The major source of microbial ingression and subsequent evolution of biofilm on the catheter body is the skin surface at entry and catheter hub, which move along the catheter surface and cause bloodstream infections.[26,27]

The prospective risk factors for CRBSI are existing disease conditions, catheter insertion techniques and the reason for the usage of catheters. The probability of CRBSIs multi-fold when nutritional products are administered through intravascular catheters. Inadequate personal cleanliness, moisture near the exit site and concurrent ailments acts as local risk factors in the pathogenesis of these infections.[3]

The extent of more than one CRBSI in a patient receiving prolonged parenteral nutrition can involve the development of liver failure related to parenteral nutrition and may raise the risk of intestine transplantation.[28,29] The common pathogens causing CRBSI are coagulase-negative staphylococci, *Staphylococcus aureus*, *Candida* spp and *Pseudomonas aeruginosa*.[30]

CRBSIs are the type of nosocomial infections that are considered as the first and most preventable one. Usage of sterile barriers during catheterization by adopting principles of hand cleanliness, skin antisepsis, regular inspection of catheterization sites, records of catheterization and de-catheterization dates, maintaining shut systems, replacement of catheters if symptoms of infection observed and rinsing of catheter lumens with saline can avoid episodes of CRBSI.[31,32]

Biofilm

Microbial biofilms on implanted medical equipment arise as a result of infections brought on by bacteria transmitted from patients and healthcare workers.[33]

A biofilm is a well-established cluster of infective microbes, extracellular products, and host components that are entrapped in a medium of extracellular polymeric substances.[34,35] Once the biofilm is formed, microbes acquire antimicrobial resistance and increased doses of antibiotics may still not be enough to eradicate the germs inside the biofilm. [22]

Most of the organisms that grow into biofilms on implantable devices are yeasts and bacteria, either gram-positive or gram-negative. The main pathogenic organisms detected from these devices are *S. aureus, E. faecalis, S. epidermidis, and Streptococcus viridans* among gram-positive; *Escherichia coli, Proteus mirabilis*, *Klebsiella pneumoniae, and P. aeruginosa* among gram negative. Based on the type of device and duration of implantation, the medical devices may get contaminated by single or multiple types of organisms. The deposition of microorganisms on the catheter body is irreversible. This irrevocable adhesion is determined by the physico-chemical characteristics of the catheter's surface as well as the type and number of organisms in the fluid medium to which the catheter is exposed. These cells form an irreversible attachment and begin synthesizing extracellular polysaccharides in order to form a biofilm.[36]

Innovations and future directions

For hospitalized patients requiring long-term treatment, CRBSI is an omnipresent hazard. The frequency of occurrence of CRBSI can be brought down to an extent by adopting aseptic techniques and care while handing the devices. But this does not suffice in controlling the infections. Lot of innovations and approaches have been developed and are in the pipeline to prevent and combat CRBSI.[37]

Coated/ impregnated catheters

Many technological innovations are being investigated aiming at declining the incidence of biofilm development and CRBSI. One of the innovative studies involves coating or impregnating central venous catheters with antibiotics or antiseptics.[38] Coating or impregnating catheters with antimicrobial compounds exhibits considerable potential in preventing catheter-associated problems, in addition to basic preventative hygiene measures.[39]

Minocycline-rifampicin central venous catheters

The minocycline–rifampicin (MR) have broad-spectrum inhibitory activity and the CVC coated with this are the most studied devices.[40] The effectiveness of these coatings against *C. albicans*, gram-negative and gram-positive bacteria is investigated in both *in-vitro* and *in-vivo* settings. The outcomes demonstrated how well these CVCs worked to stop the common

bacteria that cause CRBSI from adhering to one another and forming biofilms, including those that are drug-resistant.[41] Review results showed that, as in contrast to non-impregnated conventional CVCs, antimicrobial-coated CVCs significantly reduce the chances of CRBSI in kids under the age of 18.[42]

H Y Chong, N M Lai *et al.*[43] compared the rate of CRBSI reduction of MR-impregnated CVC against uncoated CVCs. The results showed that MR-impregnated CVCs significantly reduced CRBSI. This recommends that the MR-impregnated CVCs are better alternative for averting CRBSI.

Issam Raad, Rabih Darouiche *et al.*[44] discovered that no patients developed CRBSI with MR coated CVCs compared to uncoated catheters.

A study conducted by Leonardo Lorente, Maria Lecuona, *et al.*[45] aimed to compare the incidence of CRBSI between the usage of ordinary plain catheters and catheters impregnated with RM. The regular plain catheters showed a greater CRBSI episode than RM-impregnated catheters.

This proved the effectiveness of coating catheters with MR against the incidences of CRBSIs along with zero adverse events and with no drug resistance, by avoiding the incidences of CRBSI, the ultimate medical cost can be reduced.

Chlorhexidine and silver sulfadiazine central venous catheters

Hongliang Wang, Hongshuang Tong *et al.*[5] reviewed the usefulness of antimicrobial-coated CVCs for averting CRBSI. In this review, 10,464 patients from 33 trials were included. Compared to standard catheters, Chlorhexidine and silver sulfadiazine (CHSS)-infused catheters showed a decrease in the amount of CRBSIs per 1000 catheter days of use as well as a lower rate of colony formation on the catheter. The catheters impregnated with CHSS or other antibiotics are greater tools in averting infections than standard catheters.[5]

The effectiveness of CHSS-impregnated CVC against clinical isolates of *C. albicans, C. glabrata, C. parapsilosis* and other developing non-albicans was investigated by L. Cobrado, A. Silva-Dias, *et al.*[46] In biofilm formation assays and semi-quantitative XTT reduction assay, the CHSS coated CVC showed inhibition ranging from 60% to 100%. CHSS catheters can effectively prevent the biofilm development by Candida species.

Leonardo Lorente, Maria Lecuona *et al.*[47] demonstrated that CRBSI and its associated cost can be lowered with CHSS impregnated catheters than plain uncoated catheters.

Rifampin-miconazole central venous catheters

Leonardo Lorente, Maria Lecuona *et al.*[48] studied the venous catheterization at femoral and central jugular veins, the prevalence of CRBSI linked with RM-impregnated catheters and plain uncoated catheters. The incidences of CRBSI associated with Rifampin-miconazole (RM)-impregnated catheters was lesser than standard catheters in patients with shorter duration of catheter use.

Yucel N, Lefering R *et al.*[6] carried out a study on 223 adult hospitalized patients with MR coated catheters. The infection observed with MR-coated catheters is 4.2 and 17.1% in standard. MR coated catheters were devoid of adverse effects and no resistance to antimicrobial agent was observed and proved to be having considerably lesser risk of bacterial colonisation and CRBSI in comparison with plain uncoated catheters.

Fluoro uracil (5-FU) central venous catheters

JM Walz, J Luber *et al*.,[49] J Matthias Walz , Rui L Avelar *et al*.[50] and R. Avelar, A. Jonker *et at.* [51] proved the effectiveness of CVC coated with 5-FU, against the development of CRBSI. The 5-FU coated catheters were effective in diminishing the development of biofilm. In a larger animal model, the content of 5-FU from the 5-FU coated CVC was undetectable in the serum and the nil episodes of toxicity in the tissues at the implantation site. It is concluded that 5-FU can be a significant agent for reducing infections related to catheter usage after considering the safety and effectiveness demonstrated in this investigation.

In a study, the conventional poly urethane catheters with one, two, or multi-lumen were compared with the catheters coated with antibiotics like miconazole/rifampicin, 5-FU, benzalkonium chloride, teicoplanin, minocycline, and minocycline/rifampin. In 1000 catheter days, the incidences of CRBSI and bacterial colony formation were lower with the antibiotic-coated catheter proving its greatest potential and are better than the conventional catheters in averting CRBSIs.[5]

Gendine-coated central venous catheters (combination of gentian violet and chlorhexidine)

The gendine-coated catheters and endotracheal tubes showed inhibitory activity against various pathogenic organisms up to 3 weeks. The duration, antimicrobial effectiveness and wide spectrum of activity was elevated against the organisms responsible for urinary tract infection and pneumonia. Moreover, it was demonstrated that these coated devices are non-cytotoxic.[52]

The protection against bacterial adherence shown by gendine-coated central venous catheter against methicillin-resistant *P. aeruginosa* and *S. aureus* was found to be considerably higher than other CVCs. Compared to CVC impregnated with antibiotics or with metal ions and carbon, gendine-coated CVC demonstrated superior protection against *C. albicans* and *C. parapsilosis*. After being soaked in serum for 28 days, the gendine-impregnated CVCs continued to exhibit antibacterial activity against *MRSA, P. aeruginosa, and C. parapsilosis*.[53]

Upon testing the gendine-coated catheters in an intravascular model of rabbit against standard catheters and comparing for the *in-vitro* efficacy against different pathogens with minocycline/rifampin, and chlorhexidine-coated catheters, the gendine-coated catheters wholly averted CRBSI-causing pathogens from attaching to biofilm. The gendine-coated catheters effectively prevented the harmful bacteria and fungi's ability to produce biofilm. Gendine catheters were found to be biocompatible and gentian violet from the gendine catheters were well within safe levels.[54]

Boron carbon nitride nanocoating central venous catheter

Nano coating of boron carbon nitride was established on CVCs and the antimicrobial activity of these catheters were studied. The boron carbon nitride nanocoating showed better anti-biofilm activity, lesser colonization rate, reduced episodes of CRBSI and averted the establishment of antimicrobial resistance. Reduced CFU formation and suppressed biofilm development were observed for *E. coli,* and for *B. cereus*. [55]

N-acetylcysteine-levofloxacin central venous catheters

Mohammad D. Mansouri, Richard A. Hull *et al*.[56] examined the *in-vitro* antibacterial properties of CVCs impregnated with N-acetyl cysteine-levofloxacin and N-acetyl-cysteine. The N-acetylcysteine-levofloxacin catheters showed successful results in eradicating both gram-positive and gram-negative organisms and drastically declined colony formation, declaring the efficiency of this combination to avert CRBSI.

Antimicrobial lock therapy

For the patient population which can be at great threat of acquiring CRBSI, antimicrobial lock therapy can be considered. Generally, the solution of antimicrobial lock therapy (ALT) includes a 2 to 4 mL of a concentrated antibiotic liquid [100–1000 times higher than the MIC] which can be locally instilled into the catheter of the lumen. This liquid may contain an anticoagulant. The liquid is allowed to reside when the CVC is not in use. This prevents colonization and also aids in sterilizing the already infected catheter. The luminal colonization and ensuing CRBSI can be prevented by ALT.[57] Typically, the CVC lumen is filled with an antibiotic solution at a high concentration or at its customary target systemic concentration.[58,59]

In a rabbit model and in hemodialysis patients, minocycline-EDTA (M-EDTA) flush solution was found to be efficacious in eradicating fungal and bacterial biofilms and effectively preventing catheter-related infection and colonization.[60]

Tests conducted *in-vitro* against fungi, gram-positive and gram-negative organisms on a lock solution including citrate, methylene blue, and parabens showed a synergistic impact with high antimicrobial activities.[61]

The efficiency of using 70% ethanol lock or saline solution with heparin is studied for the aversion of blood infections in patients catheterized at the subclavian vein. Ethanol locks hold great promise in preventing catheter infections, and they should be investigated in a larger number of patients with various intravascular catheter reasons. They may also considerably lower bacteremia in those with compromised immunity.[62]

The taurolidine successfully removed pathogens from non-tunneled and tunneled catheter biofilms:citrate: heparin lock solution, which also assisted with preserving catheter lumen sterility.[63]

Teicoplanin lock therapy is a safe and effective treatment for catheter-related infections caused by MRSA; its total port survival rate was 72.7%.[64]

When coagulase-negative staphylococci are found, systemic antibiotics in conjunction with linezolid lock therapy are developed for pediatric cancer patients and investigated as an option for therapy for CRBSI and a way to extend CVC survival.[65]

An ALT with a novel approach was developed with a nitric oxide donor attached to ampicillin. The biocompatibility of this ALT was accessed by hemolysis and cell compatibility studies. The investigation demonstrated the ALT's potential in treating bacterial infections on CVC by combining the actions of nitric oxide and ampicillin.[66]

Alteration of the catheter's polymeric surface

The usage of polymers gained momentum in a variety of areas due to their excellent physico-chemical properties and adaptability. They are widely used in artificial valves, prosthetic hips, controlled drug delivery devices and various medical instruments. Medical devices can be developed with surface modification of polymer without altering the inherent properties. The most popular methods for altering PVC device surfaces include flame treatment, chemical grafting, electric discharge, plasma treatment, corona discharge, vapor deposition of metals, flame treatment, direct chemical modification (oxidation, hydrolysis, etc.), and even minor alterations in the roughness of the surface.[67]

Surface modification was carried out on silicone and antimicrobial peptides with polyvinyl pyrrolidone-coated silicone. The antibacterial and anti-biofilm properties of these catheters were demonstrated against *P. aeruginosa, E. coli* and *S. aureus*.[68]

Surface-modified polymer brushes of polyurethane with surface-modified poly (3 - [dimethyl-[2 - (2- methylprop -2 - enoyloxy) ethyl] azaniumyl] propane -1- sulfonate brushes as the lower layer and antimicrobial peptide-conjugated poly (methacrylic acid) brushes as the upper layer shown outstanding bactericidal properties against both gram-positive and gram-negative bacteria, and it was able to stop the build-up of bacterial debris on surfaces. They were low cytotoxic and had strong hemocompatibility.[69]

Surface modification of polyurethane surfaces with hypericin nanoformulations coating showed a reduction in bacterial growth and averted the establishment of biofilm *in-vitro*. The bactericidal impact of photodynamic treatment was enhanced by the additional application of ultrasound, reaching a maximum effect of 99.99998% eradication.[70]

Novel drug delivery systems

The limitations of coating or impregnating the catheter surface include insufficient drug absorption at the surface or slow or fast, or uncontrolled release of drug in the initial hours after catheter insertion. The lipid and polymer-based novel drug delivery systems may be used as an alternative for preventing colonization and biofilm formation on biomedical devices.[71]

Drug encapsulated liposomes

A liposomal hydrogel system with polyethylene glycol gelatin with sequestered ciprofloxacin reduced the adherence of microbes on the catheter surface. These hydrogels were cross-linked. The elution of ciprofloxacin was good enough to show

antimicrobial efficacy against *P. aeruginosa* over seven days. The *in-vitro* adhesion assay showed the inhibition of bacteria getting adhered to the catheter surfaced during the entire duration. There is potential for this novel antimicrobial coating to prevent and or treat infections related to catheter usage.[72]

By creating cross-links between the gelatin gel and coating it to medical equipment, liposomes with a sustained release property were produced. Seven out of nine cases in the *in-vivo* trials with a catheterized rabbit model of urinary tract infection showed no viable *E. coli* on coated catheter surfaces, while all seven untreated catheter surfaces were contaminated.[73]

In eliminating antibiotic-resistant *P. aeruginosa* isolates dwelling in a biofilm, the new liposomal gentamicin formulation with gallium metal has shown to be more efficient than gentamicin alone.[74]

The effectiveness of amphotericin B lock therapy in liposomal formulation was evaluated in children with fungal catheter related bloodstream infections with promising results.[75]

The *in-vitro* susceptibility of liposomal amphotericin B and anidulafungin antifungal lock therapy to *C. albicans* and *C. glabrata* biofilms was investigated in a rabbit model. Both of these anti locks showed promising result against infections related to catheter usage due to *C. albicans* strains. However, when it came to the *C. glabrata* strains, anidulafungin out performed liposomal amphotericin B in terms of activity.[76]

Bacteriophages therapy

Bacteriophage therapy is a useful tool in the treatment of biofilm-induced CRBSI due to the advantages of site specificity without being toxic to host cells and also inexpensive. It does not affect the normal microflora of the host. It can improve the treatment of CRBSI with conventional antibiotics.[77]

Before the innovation and prevalent use of antibiotics, infections caused by bacteria were averted and/or treated by using bacteriophages. Bacteriophage treatment was suggested as an approach to manage bacterial biofilms.[78]

In order to address the issue of bacterial biofilms and to avert antimicrobial resistance, bacteriophages were developed. These phages act by degrading the enzymes on the biofilm and concomitantly attack microbial cells and extracellular polymeric substances of the biofilm. The enzymatic phage significantly decreased the numbers of bacterial biofilm cells by 99.997%, which was approximately two orders of magnitude better than that of the non-enzymatic phage.[79]

Bacteriophages with antibiotics appear to be a good approach to abolishing biofilms *in-vitro* or *in-vivo*. According to the research, phages, and lysins by themselves or in conjunction with antibiotics may be a potent weapon against the *in-vivo* and *ex-vivo* production of biofilms.[80]

The bacteriophages are efficient in bringing down the drug-resistant biofilm of *P. mirabilis*. The phages are efficient in 99.9% disruption and reduction of biofilms. One approach that is seen to be promising for treating biofilm infections brought on by isolates of *P. mirabilis* that are resistant to drugs is the use of bacteriophages.[81]

Polymeric carriers

Various approaches are being devised for incorporating antimicrobial properties in polymeric medical devices. These polymers are now being infused with a variety of possible antibacterial agents.[82]

The usage of biodegradable polymers from both animal and natural sources has gained a perceptible consideration for being used as carriers. Among these, important ones are hydrogel-type materials, micelles and microspheres with polymers that are efficient nanocarriers. These can improve the absorption rates, decrease systemic drug toxicity, and protect pharmaceuticals from biochemical degradation.[83]

Delivering the antimicrobial agent to the site of action and preventing it from losing its effectiveness through interactions with other molecules are the primary functions of polymeric carriers. Additionally, polymeric carriers are employed as controlled release mechanisms to improve the efficacy of drug therapy.[84]

The development of biodegradable polycarbonates functionalized with guanidinium has shown a broad range of antibacterial activity *in-vivo*, making them suitable for application against infections resistant to multiple drugs. These macromolecules exterminated the bacteria without altering the morphology of the membrane. An efficient *in-vivo* activity was established against multidrug resistant infections in mouse models of *A. baumannii*, *E. coli*, *K. pneumoniae*, *MRSA* and *P. aeruginosa*. These macromolecules remained non-toxic.[85]

Glass slide coatings with switchable characteristics based on arginine polymers demonstrated better antibacterial efficacy along with stability, durability and biocompatibility.[86]

Antimicrobial peptides

A new family of synthetic and natural peptides, called antimicrobial peptides, is an emerging strategy that can target a variety of organisms, including bacteria, fungi, viruses, and parasites.[87]

These are tiny, naturally occurring peptides that are essential parts of the host immune system. The antimicrobial peptides were developed due to the advent of microbes resistant to drugs. [88]

A synthetic human antimicrobial peptide with enhanced antimicrobial and anti-biofilm properties was developed. This peptide stopped biofilm formation and eradicated developed biofilms.[89]

Melimine and Mel4 antimicrobial peptides, when attached to the surfaces, were effective in diminishing the infection in both humans as well as animals without being toxic to host cells. Antimicrobial peptides are covalently bound to polyvinyl chloride *via* plasma immersion ion implantation, shown to have strong antibacterial action and lower bacterial adherence.[90]

In rat CVC infection models, synthetic antimicrobial peptides like omiganan, Bac8c, WMR, HB43, P18, Ranalexin, and polyphemusin were efficacious against *S. aureus* biofilm. For the treatment of *S. aureus* intravenous catheter infections, they can be utilized either alone or in conjunction with other antimicrobial peptides.[91]

Electrical enhancement of antimicrobial activity

Electrical current can be used to demonstrate a phenomenon known as the "bioelectric effect", which helps in averting biofilm formation and boost anti-biofilm activity.[71]

In-vivo S. epidermidis-induced osteomyelitis rabbit model was used to study the anti-biofilm activity of low-voltage electrical current. This demonstrated that low amperage electrical current has bactericidal effects.[92]

A CVC with two electrodes having conductive elements and separated by a non-conductive segment was developed and incubated with *S. aureus* at pre-determined current levels. The microbes were reduced considerably for a duration of 8 hours. Furthermore, compared to the untreated catheter, the treated catheter exposed to electrical current contained noticeably fewer microorganisms.[93]

An *in-vitro* catheter model with low-amperage direct electrical current was studied for 24 hours of 500 μA against *C. parapsilosis, S. epidermidis, S. aureus*, *E. coli* and *P. aeruginosa* biofilms which were grown inside the polyvinyl chloride catheters. No viable bacteria were detected in the biofilms of S. *epidermidis* and *S. aureus* when exposed to direct current.[94]

CONCLUSION

The matter brushed up in this article emphasizes central venous catheters, various types, their insertion sites, formation of biofilm, subsequent CRBSI and impediments arising with the usage of them. Hitches related to CVCs are most prevalent and are the main reason for severe mortality and morbidity. Numerous regulations can lower the costs and morbidity linked to central venous catheters. It also emphasized the novel approaches developed with the aim of combatting CRBSI. Several studies have highlighted the benefits of coated/impregnated catheters, and modification of catheter surface to avert the development of biofilm and its linked complications. There are several leading brands of coated/impregnated catheters available in the market. The evidence seems overwhelmingly in favor of the usage of coated catheters along with strict hand hygiene and they have even proven to be cost-effective by avoiding adverse events.

According to all previous studies, the review advocates that CRBSI can be controlled by adopting novel approaches. Apparently despite these innovations, there is an imperative need for larger research in the development of modified CVCs and also to evaluate clinically to combat the CRBSI completely.

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