Journal of Pharmaceutical Research and Innovation (JPRI)
Vol-3, Issue-1, January 2023

e-ISSN: 2583-0023

A Review on Potential Applications of Phage-Based Binding Affinity in Antibacterial Catheter Nanocoatings

Monisha Krishnan [1*], Lakshmi Narasimman V [2]

[1] Department of Microbiology, Rathnavel Subramaniam College of Arts and Science, Coimbatore, Tamil Nadu, India
[2] Department of Microbiology, Sri Vijay Vidyalaya College of Arts and Science, Krishnagiri, Tamil Nadu, India
*Corresponding Author Email: monishak4477@gmail.com

Abstract

Catheter use in debilitated patients often precedes a number of nosocomial infections by bacterial strains that show multidrug resistance or total drug resistance, particularly through biofilm formation. Common etiological agents include Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Escherichia coli, Salmonella spp., Klebsiella spp., Acinetobacter baumannii, and Burkholderia cepacia. As catheters provide exposure to typically sterile environments, fomites and aerosols are able to transfer severe infection to the affected patients, particularly due to their immunocompromised states. The catheters may be coated using a hydrogel layer containing immobilized bacteriophages, yet different approaches may be used, including stratification, serial activation of strata, liquid nanocoatings, diffusible membranes, multi-receptor bacteriophages, and the use of lytic and lysogenic phages should be distinguished. The multifaceted growth requirements of the bacteria additionally allow for factors such as pH and temperature to be utilized in the hydrogel layer through absorptive action once bacterial attachment to the layer occurs. Moreover, nanocoating is aimed at preventing the colonization of numerous bacterial cells, thus inhibiting quorum sensing ability of the bacteria and biofilm formation.

Keywords

Affinity, antimicrobial resistance, bacteriophages, biosensors, microorganisms.

INTRODUCTION

Antibiotic resistance is a growing trend in the biomedical field that is becoming more crucial as time continues. Although a number of new antibiotics are synthesized in the laboratory, the development of resistance to the compounds is growing rapidly as well. Antibiotic resistance often takes root at the genetic level, where exposure to microbicidal agents provide selective pressure that promotes mutations in bacterial cells, which undergo rapid multiplication. The onset of evolution is thus expedited over the generations of bacterial growth, where an organism such as *Escherchia coli* has a doubling time of 20 minutes. The most notable examples of multidrug resistant (MDR) bacteria of concern are *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella* spp., *Klebsiella* spp., *Acinetobacter baumannii*, and *Burkholderia cepacia* [1].

Microorganisms are known to cause infections by two mechanisms, either encrustation or biofilm formation. Biofilm formation is a known mechanism by which organisms produce extracellular polysaccharides that facilitate adherence to the catheter and thus colonization occurs, where antimicrobial substances are reduced in diffusion ability. The biofilms increase resistance of the microorganisms by allowing them to grow slowly and making them hard to kill. Encrustations are especially observed in cases of urinary catheters, particularly in relation to urease-producing microorganisms, such as *Proteus mirabilis*. These opportunistic pathogens convert urea from urine to ammonia and organic compounds, producing them in the form of crystals which cause occlusion of the catheter. Both routes of pathogenesis are accelerated by lesions caused by frictional movement of the catheter within the mucosal tracts [2][3].

Patients most severely affected by such MDR strains are frequently immunocompromised and immunosuppressed individuals, especially those who receive in-patient treatment at hospitals and care homes. Nosocomial infections are hospital-acquired infections that are often caused by opportunistic pathogens, which are microorganisms normally living as commensals but become highly pathogenic when they gain entry to normally sterile parts of the human body. Routes of entry include post-surgical wounds, infected dressings, intravenous catheter use, and aerosol transmission from hospital personnel. The focus is now shifting to the development of nanocoatings on catheter surfaces that incorporate antimicrobial substances or particles such as viruses or enzymes. Bacteriophages are viruses that kill bacteria and are specific to their targets, allowing for the human cells to remain intact. Such phages can be employed to either kill the bacterial cells by infection or an apoptotic gene which causes cell death once inserted successfully [4][3].

Journal of Pharmaceutical Research and Innovation (JPRI)
Vol-3, Issue-1, January 2023
e-ISSN: 2583-0023

TYPES OF COATING MATERIALS

Biomaterials may be specifically designed for coating peripheral IV catheters for use within the narrow parameters of the veins or urethra. Engineered hydrogels have been shown to reduce biofilm formation by nearly five-fold [5]. General types of coatings include:

Metal Nanocoatings

They are convenient, where a simple layer can be coated onto the surface of the catheter. They exhibit fair levels of antimicrobial activity based on their ionic activity and simultaneous oxidation and reduction reactions at the cell wall. However, the possibility of metal poisoning, such as in the case of copper coatings, deters their use, while iron based materials may affect the hemoglobin levels upon availability, as well as provide the content required for fungal iron sequestration, thus enhancing fungal growth and infection into deep tissue. Most importantly, the issue of chemical reactions between tissue or other biological fluids is a major risk. Silver coatings are looked at for efficacy and have been claimed to show no cytotoxicity in the host [6].

Hydrogel Nanocoatings

They can be made thin and are often suitable for biological uses. They also contain micropores for interchange of microorganisms and particles. Pores should be adjusted to ensure that the phages do not detach from the medium. The gel is hydrated, allowing for water particle pockets that allow for permeation to greater extents compared to other materials [7]. It allows for the movement of bacteria and viruses at once; injectables can be produced easily due to the biodegradability and distribution properties of the alginate-based biomaterials. Examples are agar, agarose, alginate, etc.

Diffusible Membranes

They are also thin and can be made with uniform structure and pore distribution. Concentration gradients can be used to make such a structure functional, yet the advantage is that nanopores will not allow entrapment of bacteria from the biological fluids. Cellulose-based membranes may be used since they do have virus-retention properties.

Liquid Coatings with a Solid Interface

They allow for interaction with phage particles; attachment by specific binding or adsorption is taken care of while fluid components are able to be used for either pH or temperature regulation. It takes on a one-sided arrangement of thickness since hydrogel coatings are those with even distribution of air and water bubbles, unlike these, which resemble double layered beds [8].

Liquid Coatings

They are easily applied but may be easily worn off by the flow of biological fluids or absorbed into the body itself, making it short-lasting. The viscosity of the coating may differ, yet the exposure of the virus particles to the microenvironment fluids is a shortcoming.

PHAGES FOR ATTACHMENT: METHODS FOR BACTERIAL LYSIS

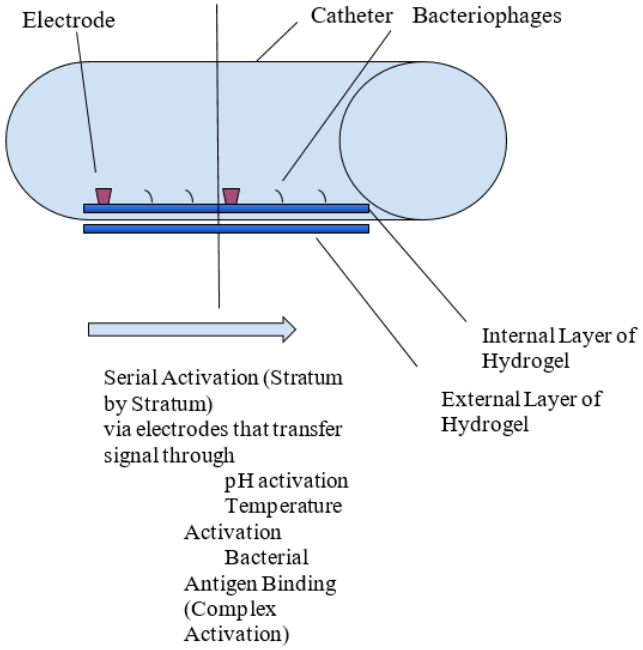

Figure 1. Schematic diagram of catheter with serial activation feature

Bacteriophages are specific to the bacteria they attack, thus being able to be used as either direct lysis agents or a way for bacterial attachment which pulls them in for the nanocoating to cause lysis through either direct toxicity or unfavorable conditions. The activation of the bacteriophage release can be induced using different factors which include.

pH

The concentration of hydrogen ions comprises pH, a measure of alkalinity or acidity. The coating can be specialized in such a way that the material changes pH when bacteria are in contact or close proximity, perhaps releasing bacteriophages by partial dissolution of the coating. Formation of crusts and blocks in urinary catheters have been avoided by the use of bacteriophages which were released by pH activation [9].

Stratification

The breaking of the catheter into segments will allow for serial activation of the coating in different regions of the human body, where one region experiencing bacterial lysis due to contact can offset the release of phages in the next segment.

Phages adhere to bacterial cells with specificity and cause lysis when the bacterium produces more phage particles. When lysis occurs, bacterial cells burst open, allowing for release of different factors, peptides, and enzymes that can thus activate the next segment of the coating by either changing the pH or other conditions of the coating to entrap

e-ISSN: 2583-0023

or lyse the bacterium. The lysis of the bacteria in one part of the coating shall cause a change in that segment that can spread to adjacent segments as a diffused effect [3].

Temperature

The intrinsic properties of the nanocoating can be adjusted easily, particularly if a hydrogel coating, where components can be used to cause micro-heating or micro-cooling that destroys MDR strains located in that specific region of the body. The bacteria can be reacted with using miniscule electrical pulses or ultrasound that destroys the cells. A majority of these treatments will destroy the cell wall and denature proteins simultaneously. It has been observed that some bacteriophages were able to tolerate 70°C, allowing for temperature to be a supplementary factor [2].

Inert Coating

Bacteriophages can be made to project from the coating of the catheter and thus lyze the bacteria they come in contact with. Limiting factors include the number of phages. Either low numbers of phages can be used or replication-controlled viruses should be utilized in order to control their generation when infecting bacterial hosts and multiplying. The phages can also carry genes that are inserted into the bacterial genome and lyse the cells or cause major metabolic failure, as is applied in gene therapy [3].

Redox Reactions

Once bacteria are absorbed into the coating, they can be lysed by oxidation and reduction reactions, using substances such as pyocyanin which prevents the growth of bacteria besides *P. aeruginosa* due to its generation of reactive oxygen species which destroys the cells immediately. There are already existing catheters with redox coatings that are designed by aligning a series of electrodes with a sensing region, such as that credited to the University of Hull (US20100016699A1).

Enzymes

They can be incorporated into the coating to ensure lytic functions, such as cell wall lysis or destruction of the genetic material in the nucleoid, inhibiting bacterial replication. Examples are lysozyme analogues which are preferably bacterium-specific, including acylase and alpha-amylase. However, care should be taken not to allow enzymes that lyse the viruses that are incorporated as well [10].

Antibacterial Substances

Antibiotics have been incorporated by impregnation of the catheters for decades, yet development of resistance to rifampin and minocycline has been a constant concern. They show a decreased colonization rate around the catheter in ICU patients with leukemia, trauma, and other illnesses [8].

BIOSENSORS

There have already been bilayer models of catheter coatings in which the upper layer reacts with pH-altered urine to dissolve the polymer coating and react with the underlying layer which contains a dye. This mechanism leads to advanced warning of the catheter blockage by urine crystals, developed for *Proteus mirabilis* infections of the catheters [5].

Biosensors convert signals from biochemical reactions into information for analysis. In this case, nanosensors that detect ammonia crystals may be adequate to indicate early blockage by passing on the signal to an external monitor. If a segmented approach is used, one segment can be used to pass on the signal to adjacent segments, leading to activation of various mechanisms, including changes in pH or redox potential. Display of phages on a solid interface may also be an activation-based response of serial activation [9].

CHALLENGES AND POTENTIAL SOLUTIONS

The effective nature of phages for different medical purposes, such as phage therapy, depends partly on the proper incorporation of phages into the biomaterial since they are sensitive to surrounding conditions over time and reduced phage titre renders them less effective, requiring planned stimuli response systems for inducible release [11]. Catheter-associated urinary tract infections involving multiple antibiotic-resistant pathogens may require phage cocktails for effective response and preventing biofilm formation leading to sepsis. For this, a phage cocktail was prepared with a broad range of target pathogens and cell viability was measured as a measure of the effect [12]. A clear model was established for such pathogens through a phage cocktail prepared against biofilm-forming *Proteus mirabilis* and the pathogenic quorum sensing mechanism, effectively quenching surface colonization [13] and proving effective against more than one biofilm-forming species [14], as well as in cases of opportunistic infections or excessive growth of certain microorganisms [15].

Greater focus on modes of delivery and concentration of phages *in vivo* could be greatly beneficial to targeted organisms in the human body, particularly at different sites in the digestive system and at other organs [16]. Overall, metal-coated catheters have shown inconsistency in clinical trials and alternatives, such as bacterial interference, microbe responsive coatings, and combination therapies are being explored as newer options for reducing UTIs [17]. When biosafety is considered, the same biomaterials containing stabilized phages can be injected directly into a patient for therapeutic purposes, such as alginate hydrogel injectables which show good biodegradability properties and local distribution [18]. Based on synergistic effects of the phages and antibiotics toward biofilm-forming *Klebsiella* sp., bacteriophage-based therapies are one of the most feasible options to counter multi-drug resistance and provide a last resort to cases where antibiotics do not prove effective [19]. Catheters have also been coupled with biosensors for pathogenic infections in urinary tracts which could signal microbial invasion and colonization before they advance into septic conditions [20].

e-ISSN: 2583-0023

CONCLUSION

For the future prevention of MDR bacterial infections due to catheter use, the designing of new coatings is an ideal solution, granted that the ideal material is determined based on the biological conditions which the coating will make contact with. Replication-controlled phages or low numbers can also minimize the effect on the microbiota, unlike the non-specific effect that antibiotics show in the human microbiome.

Conflicts of Interest

There are no conflicts of interest.

Author's Funding

This work received no specific grant from any funding agencies.

REFERENCES

[1] Fayez, Mohamed & Hakim, Toka & Agwa, Mona & Abdelmoteleb, Mohamed & Aly, Rania & Montaser, Nada & Abdelsattar, Abdallah & Rezk, Nouran & El-Shibiny, Ayman. (2021). Topically Applied Bacteriophage to Control Multi-Drug Resistant Klebsiella pneumoniae Infected Wound in a Rat Model. Antibiotics. 10. 10.3390/antibiotics10091048.

[2] Donlan RM. Biofilm formation: a clinically relevant microbiological process. *Clin Infect Dis.* 2001;33:1387–1392

[3] Singha, P., Locklin, J., & Handa, H. (2017). A review of the recent advances in antimicrobial coatings for urinary catheters. Acta biomaterialia, 50, 20–40. https://doi.org/10.1016/j.actbio.2016.11.070.

[4] Nikaido H. (2009). Multidrug resistance in bacteria. *Annual review of biochemistry*, *78*, 119–146. https://doi.org/10.1146/annurev.biochem.78.082907.145923.

[5] Milo, S., Thet, N. T., Liu, D., Nzakizwanayo, J., Jones, B. V., & Jenkins, A. T. A. (2016). An in-situ infection detection sensor coating for urinary catheters. *Biosensors & bioelectronics*, *81*, 166–172. https://doi.org/10.1016/j.bios.2016.02.059.

[6] Paladini, F., Pollini, M., Deponti, D., Di Giancamillo, A., Peretti, G., & Sannino, A. (2013). Effect of silver nanocoatings on catheters for haemodialysis in terms of cell viability, proliferation, morphology and antibacterial activity. *Journal of materials science. Materials in medicine*, *24*(4), 1105–1112. https://doi.org/10.1007/s10856-013-4870-0.

[7] Wroe, J. A., Johnson, C. T., & García, A. J. (2020). Bacteriophage delivering hydrogels reduce biofilm formation in vitro and infection in vivo. *Journal of biomedical materials research. Part A*, *108*(1), 39–49. https://doi.org/10.1002/jbm.a.36790.

[8] Wassil, S. K., Crill, C. M., & Phelps, S. J. (2007). Antimicrobial impregnated catheters in the prevention of catheter-related bloodstream infection in hospitalized patients. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*, *12*(2), 77–90. https://doi.org/10.5863/1551-6776-12.2.77.

[9] Milo, S., Hathaway, H.J., Nzakizwanayo, J., Alves, D.R., Esteban, P.P., Jones, B.V., & Jenkins, A.T. (2017). Prevention of encrustation and blockage of urinary catheters by Proteus mirabilis via pH-triggered release of bacteriophage. *Journal of materials chemistry. B, 5 27*, 5403-5411 .

[10] Yassin, M. A., Elkhooly, T. A., Elsherbiny, S. M., Reicha, F. M., & Shokeir, A. A. (2019). Facile coating of urinary catheter with bio-inspired antibacterial coating. Heliyon, 5(12), e02986. https://doi.org/10.1016/j.heliyon.2019.e02986.

[11] Malik, D. J., Sokolov, I. J., Vinner, G. K., Mancuso, F., Cinquerrui, S., Vladisavljevic, G. T., Clokie, M. R. J., Garton, N. J., Stapley, A. G. F., & Kirpichnikova, A. (2017). Formulation, stabilisation and encapsulation of bacteriophage for phage therapy. Advances in Colloid and Interface Science, 249, 100–133. https://doi.org/10.1016/j.cis.2017.05.014 .

[12] Sanchez BC, Heckmann ER, Green SI, Clark JR, Kaplan HB, Ramig RF, Muldrew KL, Hines-Munson C, Skelton F, Trautner BW and Maresso AW (2022) Development of Phage Cocktails to Treat E. coli Catheter-Associated Urinary Tract Infection and Associated Biofilms. Front. Microbiol. 13:796132. doi: 10.3389/fmicb.2022.796132.

[13] Ryan, E. M., Gorman, S. P., Donnelly, R. F., & Gilmore, B. F. (2011). Recent advances in bacteriophage therapy: how delivery routes, formulation, concentration and timing influence the success of phage therapy. The Journal of pharmacy and pharmacology, 63(10), 1253–1264. https://doi.org/10.1111/j.2042-7158.2011.01324.x.

[14] Lehman, S. M., & Donlan, R. M. (2015). Bacteriophage-mediated control of a two-species biofilm formed by microorganisms causing catheter-associated urinary tract infections in an in vitro urinary catheter model. Antimicrobial agents and chemotherapy, 59(2), 1127–1137. https://doi.org/10.1128/AAC.03786-14.

[15] Curtin, J. J., & Donlan, R. M. (2006). Using bacteriophages to reduce formation of catheter-associated biofilms by Staphylococcus epidermidis. Antimicrobial agents and chemotherapy, 50(4), 1268–1275. https://doi.org/10.1128/AAC.50.4.1268-1275.2006.

[16] Mirzaei, A., Wagemans, J., Nasr Esfahani, B., Lavigne, R., & Moghim, S. (2022). A Phage Cocktail To Control Surface Colonization by Proteus mirabilis in Catheter-Associated Urinary Tract Infections. Microbiology spectrum, 10(5), e0209222. https://doi.org/10.1128/spectrum.02092-22.

[17] Andersen, M. J., & Flores-Mireles, A. L. (2019). Urinary Catheter Coating Modifications: The Race against Catheter-Associated Infections. Coatings, 10(1), 23. MDPI AG. Retrieved from http://dx.doi.org/10.3390/coatings10010023.

[18] Kim, H. Y., Chang, R. Y. K., Morales, S., & Chan, H.-K. (2021). Bacteriophage-Delivering Hydrogels: Current Progress in Combating Antibiotic Resistant Bacterial Infection. Antibiotics, 10(2), 130. MDPI AG. Retrieved from http://dx.doi.org/10.3390/antibiotics10020130.

[19] Townsend, E., Moat, J., & Jameson, E. (2020). CAUTI's Next top model – model dependent klebsiella biofilm inhibition by bacteriophages and antimicrobials. https://doi.org/10.1101/2020.06.30.179804.

[20] Mach, K. E., Wong, P. K., & Liao, J. C. (2011). Biosensor diagnosis of urinary tract infections: a path to better treatment?. Trends in pharmacological sciences, 32(6), 330–336. https://doi.org/10.1016/j.tips.2011.03.001.