Catheter-associated urinary tract infections: Etiological analysis, biofilm formation, antibiotic resistance, and a novel therapeutic era of phage

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Abstract

Urinary tract infection (UTI) caused by uropathogens has put global public health at its utmost risk, especially in developing countries where people are unaware of personal hygiene and proper medication. In general, the infection frequently occurs in the urethra, bladder, and kidney, as reported by the physician. Moreover, many UTI patients whose acquired disorder from the hospital or health-care center has been addressed previously have been referred to as catheter-associated UTI (CAUTI). Meanwhile, the bacterial biofilm triggering UTI is another critical issue, mostly by catheter insertion. In most cases, the biofilm inhibits the action of antibiotics against the UTI-causing bacteria. Therefore, new therapeutic tools should be implemented to eliminate the widespread multidrug resistance (MDR) UTI-causing bacteria. Based on the facts, the present review emphasized the current status of CAUTI, its causative agent, clinical manifestation, and treatment complications. This review also delineated a model of phage therapy as a new therapeutic means against bacterial biofilm-originated UTI. The model illustrated the entire mechanism of destroying the extracellular plyometric substances of UTI-causing bacteria with several enzymatic actions produced by phage particles. This review will provide a complete outline of CAUTI for the general reader and create a positive vibe for the researchers to sort out alternative remedies against the CAUTI-causing MDR microbial agents.

Keywords: biofilm, catheter-associated urinary tract infection, multidrug resistance, phage therapy, uropathogens.

Introduction

Catheter-associated urinary tract infections (CAUTI) are nosocomial infections that have become one of the most common medical consequences. Urinary tract infection (UTI) is an infection of any organ in the urinary system, including the kidneys, ureters, urinary bladder, and urethra. A study found that indwelling catheters generate about 70–80% of complicated UTIs [1]. Several pieces of evidence have supported that the CAUTI occurred through the indwelling catheter, also known as the ID catheter [2]. The most severe issue with utilizing an ID catheter is the formation of biofilms on the device. Intermittent catheters (IC) are another medical device used to extract urine from a patient’s bladder for a short period before being removed from the patient [2]. IC is used several times a day for patients. Its setup is also needed to know correctly to avoid complications [2].

Using a catheter makes the immune-compromised (pregnant, cancer patients, older people, and HIV) patients, paraplegia patients, and patients with cerebrovascular disease [3] susceptible to UTI. In addition, once the catheter is in place, it increases the risk of UTIs by compromising the body’s primary defenses, resulting in bacteriuria, symptomatic UTI, and bloodstream infection [4].

Biofilms make CAUTI critical to treating antibiotics by generating 1000 folds of resistance against antibiotics or other chemical drugs [5]. Uropathogens could create biofilms on both surfaces of the catheter quickly. However, CAUTI occurred in both gram-positive and Gram-negative bacteria. Uropathogenic Escherichia coli (UPEC) is responsible mainly for this clinical complication. Other pathogens include E. coli, such as Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, Enterococcus faecium, Staphylococcus saprophyticus, and Pseudomonas aeruginosa [1]. Some antibiotics are commonly prescribed to treat the complications, including trimethoprim, sulfamethoxazole, ciprofloxacin, and ampicillin [1, 6].

Furthermore, bacterial transformation, metabolic activity (e.g., changes in metabolic route and efflux pump expression), drug target alteration, and drug modification contribute to increased antibiotic resistance (e.g., penicillinate). In addition, bacterial
transformation through plasmids and biofilms makes developing resistance against antibiotic drugs easier. As a result, an alternative method of treating CAUTI is required. The most promising is phage therapy, which employs the old bacterium virus combat seen in nature. Phage therapy could offer a way to infiltrate bacteria and create a precise root for treatment, individually or in combination. The causal agent for CAUTI, pathogenesis, management of CAUTI, possible treatment, antibiotic resistance, biofilm formation, and relationship with CAUTI development are discussed in this review, and phage therapy is a novel therapeutic approach.

This review aimed to provide a complete outline of CAUTI and their novel therapeutic aspect against multidrug-resistant bacterial agents.

**Catheter-associated UTI**

Patients suffering from urinary system complications such as urinary incontinence, urinary retention, and prostate or genitals surgery have been prescribed a catheter that helps drain urine into the urine bag and overcomes the difficulty, as mentioned earlier. These catheters vary in both type and size and their composition material.

Microorganisms that lead to causing this infection can be traced back to two different places. Most of them entered themselves into patients’ bodies during catheter insertion due to a lack of professionalism from the medical service provider or the surroundings [7]. Bacteria can attach and colonize the catheter tube’s surface in specific settings, spreading throughout the urinary system. Conversely, gut commensal microflora is another source of bacteria that causes this infection; it exhibits opportunistic features similar to other pathogens. However, pathogenesis through the entrance of bacteria into the body leads to periurethral colonization, urethra progression, and bladder migration. Bacteria multiply, form biofilms, epithelial aid degradation, and spread the kidney infection that cause CAUTI may also progress to bacteremia [1].

They form biofilms on the catheter’s surface, making it challenging to penetrate drugs into these biofilms. Females are 4.2 times more likely than males to be diagnosed with a UTI [8]. As CAUTI is related to hospital-acquired infection, a study demonstrated that the patients could be divided into four groups based on their age: under 65, 65–74, 75–84, and ≥85 [9]; whereas UTIs and gastrointestinal infections were shown to be more prevalent in patients over the age of 75 [10]. The complications of CAUTI can be both infectious and non-infectious. Infectious complications could be urinary catheter obstruction, bladder urolithiasis, purulent urethritis, gland abscesses, and male prostatitis. On the contrary, bacterial urethral inflammation, urethral structures, mechanical trauma, and mobility impairment occurred in non-infectious complications.

**Primary Antibiotic-resistance CAUTIs-associated Etiological Agents**

Many pathogens cause clinical complications in CAUTI. They developed antibiotic resistance due to inappropriate medications, excessive and unethical use of antibiotics in health conditions, animal reinforcement, and cultivation, all critical determinants underpinning this global crisis. Multidrug resistance (MDR) is the insensitivity or resistance to various commonly prescribed antimicrobial drugs among diverse microorganism strains (Table-1) [11, 12]. According to Centers for Disease Control and Prevention (CDC) analysis, antibiotic resistance affects nearly 3 million people in the United States [13]. Bacteria can evolve to survive against antibiotics, alter their receptor binding efficacy, and produce enzymes to degrade the antibiotics naturally. Every time new antibiotics are discovered to act against bacteria, bacteria evolve these antibiotics primarily by horizontal gene transfer. They share their mobile genetic element, such as the transposon element plasmid (through conjugation) [13]. In both developed and developing countries, it becomes hard to restrict the spread of multidrug-resistant strains. The main culprit for CAUTI referred to UPEC., *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *Enterococcus* spp., *Staphylococcus* spp., Extended-spectrum beta-lactamase (ESBL)-*Enterobacteriaceae*, Carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant enterococci (VRE), multidrug-resistant *P. aeruginosa* (MRPA), and methicillin-resistant *Staphylococcus aureus* (MRSA), CDC and WHO are concerned about the rapid spread of CRE among people in hospitals [13]. According to CDC 2019 reports, considering hospitalized data, the death tally is 9100, 1100, 5400, 2700, and 10600 persons, respectively, for ESBL-*Enterobacteriaceae*, CRE, VRE, MRPA, and MRSA. Although VRE, MRPA, and MRSA cases are decreased from the previous study, CRE cases are still stable, and an increased rate is observed in ESBL-*Enterobacteriaceae* [13]. Both UPEC and *K. pneumoniae* are expressing ESBL, making it critical to treat CAUTI [14]. Moreover, according to the WHO, 60% of bacterial pathogens, like the *Enterobacteriaceae* family, have developed resistance to widely used antibiotics, including recently isolated carbapenems and cephalosporins of the third-generation study [14–17]. Given the above results, however, it can be expected that all pathogens can gain 100% resistance [17]. However, a study reports that the increased instances of *E. coli* pathogens becoming resistant to trimethoprim-sulfamethoxazole (9–18%), cephalothin (20–28%), and ampicillin (26–34%) in the 21st century [18]. Moreover, the overexpression of penicillin-binding proteins (PBPs) with a poor affinity for β-lactams is due to intrinsic β-lactam tolerance, making *E. faecalis* 10–100 times more penicillin-resistant than *Streptococcus* and *E. faecium* 4–16 times more resistant than *E. faecalis* [19, 20]. Besides, Enterococci can quickly become immune
to antimicrobials and VRE [21]. As they are naturally resistant to trimethoprim, clindamycin, cephalosporins, and penicillins, MDR is also widespread among enterococci [22–24]. High-level resistance to glycopeptides, like vancomycin, has recently been developed by Enterococci, which is considered one of the last defense lines against multidrug-resistant species [1]. In particular, through the expression of vancomycin and teicoplanin A-type resistance (van) genes encoding the PBPs, VanA, VanB, VanD, VanE, VanG, and VanL, Enterococci developed resistance to glycopeptides [24, 25]. For VanA, the most common PBP expressed by Enterococci, the resistance mechanism is to substitute the cell wall precursor D-alanine-D-alanine with D-alanine-D-lactose, effectively reducing vancomycin’s binding affinity [25]. The worrying trend toward a high prevalence of multidrug-resistant uropathogens has prompted established alternative control measures and treatment options. However, the etiology and drug-resistant status of six major CAUTI-causing bacteria are defined as follows.

**Escherichia coli**

Uropathogenic *E. coli* is the most predominant pathogen to cause CAUTI. It reported 40–72% of CAUTI in general worldwide [7]. UPEC needs to adhere and colonize on the surface of the catheter and urinary system (bladder); these UPEC strains encode about 12 CUP pili for this purpose [1].

Furthermore, *E. coli* enters the urinary system through flagellum-mediated motility. During catheterization, *E. coli* may enter the urinary tract through the bladder, and then move out of the bladder and into the upper urinary tract, causing infection and possibly kidney infections. Moreover, UPEC displays a variety of virulence factors once it invades the body, which results in the progress and reappearance of CAUTI. The expression of type 1 fimbriae, which is present in 80–100% of UPEC strains, is one such virulence factor [2]. This adhesin helps bind UPEC and other uropathogens by uroepithelial cells lining the urinary tract and even the coating of a catheter [26]. The ability to attach to the catheter enables a UPEC infection to form, supporting the development of complex biofilms for UPEC and other strains [27]. UPEC strains have gained the ability to evade the host immune system through capsule and lipopolysaccharide (LPS) production [2]. In CAUTI, the capsules provided by UPEC perform a significant function as the capsules assist in host immune prevention, masking bacterial cells with surface structural similarity to human cells and providing immune cell resistance against phagocytosis [27, 28]. It has also been shown that capsules and LPS expression by UPEC strains help their tolerance to complement-mediated lysis and endogenous antimicrobial peptides [27, 29]. Research performed on UTI patients in Italy in 2014 showed that the rates of antibiotic resistance in *E. coli* to aminopenicillins, aminoglycosides, and fluoroquinolones were 65, 19, and 44% [30], whereas, in Bangladesh, an experiment found that *E. coli* showed very high resistance to amoxicillin 95.41%, cefradine 90.45%, and nalidixic acid 88.16% [11].

**Klebsiella pneumoniae**

*Klebsiella pneumoniae*, gram-negative bacteria, is accused of being the second-most causative agent for
CAUTI, approximating 8–16% [7]. Klebsiella pneumoniae is associated with other uropathogens to cause diseases. Klebsiella pneumoniae expresses type 1 pili to adhere to the catheter, resulting in the initialization of biofilm formation and bladder colonization [31]. The experiment proves that the FimH adhesion of K. pneumoniae is highly homologous to uropathogenic E. coli FimH adhesin though they can have different binding specificities [1]. However, the FimH adhesion of K. pneumoniae exhibits a low capability to form persistent biofilms rather than UPEC adhesins [32]. Klebsiella pneumoniae also encodes type-3 pili to promote the biofilms formations in CAUTI.

**Proteus mirabilis**

Proteus mirabilis is another Gram-negative bacterium accused of almost 5–14% of CAUTI worldwide [7]. It resulted in several nosocomial infections in sick people admitted to hospitals or receiving treatment for medical problems. Furthermore, catheterized patients are particularly vulnerable, as P. mirabilis can enter the body through catheter surfaces, most likely due to existing infestation. Multiple adherence factors, such as hemagglutinins and fimbriae, enable P. mirabilis to bind to devices with or without the presence of a conditioning film. In CAUTI, catheter encrustation/crystalline biofilm formation, the adherence capacity of P. mirabilis plays a significant role. Research showed the circumstances wherein the P. mirabilis swarm included genes and visualized cells working with each other to form smoker “cell rafts” [33]. This work explored P. mirabilis’ high motility and showed how the cells travel across a catheter surface by interweaving their flagella into helical connections to move quickly as one mass across a surface [33]. Another study also indicated that motion contributed significantly to the Virulence of P. mirabilis, leading to the migration of bacteria from the skin, catheter, and bladder [33]. It has also been found that P. mirabilis moves from the bladder to the kidneys and forms kidney stones [34]. Of all uropathogens, P. mirabilis has the highest production of urease. The urease it produces is highly reactive, hydrolyzing ammonia, like other uropathogens. Patients with nosocomial UTIs, the elderly, females, pregnant patients, and those with urinary catheterization have a high colonization frequency of P. mirabilis [1, 36]. Bacterial colonization by S. saprophiticus of the bladder and ureter epithelium occurs through many adhesive types. These involve autolytic and adhesive hemagglutinins and surface-associated lipase that forms surface appendages close to fimbria, allowing the bacteria to maintain a firm adherence to these surfaces [1]. Some strains of S. saprophiticus, especially in patients with catheters, can generate biofilms, increasing their Virulence. Antibiotic resistance is intensified after biofilms have been developed. Staphylococcus saprophiticus can be immune to vancomycin in these situations. They can only be successfully treated with linezolid [36]. Staphylococcus saprophiticus has resistance to the widely used and effective antibiotic regimens for UTIs caused by E. coli, including ampicillin, ceftriaxone, cephalaxin, and ciprofloxacin. Staphylococcus saprophiticus should be firmly suspected in cases where UTI signs
remain after treatment with one of the previously described antibiotics [35].

**Pseudomonas aeruginosa**

*Pseudomonas aeruginosa* is a Gram-negative, rod-shaped opportunistic bacteria, and around 4–12% of patients suffer from CAUTI due to *P. aeruginosa* worldwide [7]. *Pseudomonas aeruginosa* virulence is multifactorial and is due to cell-related factors such as alginate, LPS, flagellum, pilus, and non-pilus adhesins, as well as to exoenzymes or secretory virulence factors such as protease, elastase, phospholipase, pyocyanin, exotoxin A, exoenzyme S, and siderophores [38]. Although the association of these virulence factors with UTI is not well understood and studied for deep analysis. However, existing studies support the pathogenesis of *P. aeruginosa* in CAUTI depending on these virulence factors. As *P. aeruginosa* is predominant in CAUTI, it forms biofilms on the catheter. The most important component of *P. aeruginosa* biofilms is alginate, an acetylated polymer of beta-D-mannuronic and alpha-L guluronic acids. Other exopolysaccharides, such as PSL and PEL, have also been shown to play an important role in the capacity of non-alginate-forming strains of *P. aeruginosa* to shape biofilm [38]. After *P. aeruginosa* enters the body, it damages the normal mucopolysaccharide coating of the bladder epithelium, facilitates biofilm formation, and induces the Quorum sensing signal to make a microbial colony. Samples collected from UTI patients in Bangladesh found the antibiotic resistance cefuroxime (100%), cefixime (100%), and ceftriaxone (83.33%) [29]. Multidrug-resistant *P. aeruginosa* strains are also emerging worldwide [11].

**Biofilm Formation and Pathways**

Biofilm is accused of almost 60% of nosocomial infections and about 80% of microbial infections [5, 39]. Biofilm is a community of different or similar microbes in an aqueous environment surrounded by a glycocalyx matrix called extracellular polymeric substances (EPS) that acts as a glue and protects the colony from an unfavorable environment. The water channel inside the bacterial colony supports the territory with nutrients to live on the surface of cell lines, medical instruments, or, most commonly, water. An ordered structure is observed in biofilms. Microbes that form biofilms must be fulfilled some essential criteria. They can self-organize, resist environmental disturbance, be more effective, and respond as a community [5, 40]. All of the uropathogens we discussed earlier can form either individuals or combinations of biofilms.

However, the bacterial biofilm matrix consists of polysaccharides, proteins, and extracellular nucleic acid [41]; there are a few steps to developing biofilms. They are mainly attachment, maturation, and dispersion [5]. The planktonic bacterial cell is necessary to initiate bacteria’s reversible attachment to form biofilms on the targeted surface (catheter and urinary tract). The initial reversible step was the immediate touch of the traveling planktonic bacteria with the catheter [42]. This step progresses due to the availability of nutrients and increases pH for bacteria growth [42]. It happens due to the breakdown of urea into carbon dioxide and ammonia, resulting in ammonium ion with urease enzyme produced by *P. mirabilis*, *S. saprophyticus*, *Klebsiella* spp. [1]. UPEC expresses type 1 pili, antigen 43, and curli (an adhesive surface fiber) to initialize adherence (Figure-1). OxyR is a transcription regulator of antigen 43, and PrmB is a regulator of type 1 pili and curli [43]. Following events lead to the phosphorylation of PrmA and QseB [43]. Besides, urease production from *P. mirabilis* leads to crystalline biofilm formation, generating calcium and magnesium ammonium phosphate crystal (Figure-1).

RsbA upregulates polysaccharides formation of *P. mirabilis*, reducing swarming capability and promoting biofilm formation associated with the MR/P pili, which expression increases due to oxygen limitations [44]. Likewise, the MrpJ fimbrial operon regulator expression contributes to reduced motility, facilitating biofilm development [45, 46]. *Pseudomonas aeruginosa* expresses more quorum-sensing autoinducers that proliferate LasR and RhlR through binding. LasR and RhlR are transcription regulators of LasB and rhamnolipids, respectively [47].

Furthermore, the production of eDNA, rhamnolipids, lectins, elastases, and toxins proliferate through quorum sensing [1]. The amphiphilic rhamnolipids help biofilm formation by changing the hydrophobicity of *P. aeruginosa* membranes [47]. Moreover, EPS and alginites are activated by binding cyclic di-GMP with Alg44 and PelD [38, 48]. Exopolysaccharide production regulates through the small RNAs from the regulator of the secondary metabolites (RSM) family, such as rsmZ and rsmY [49, 50]. They were lowering the availability of RsmA, a transcription regulator necessary for the repression of the exopolysaccharide-encoding gene [51, 52]. During the maturation stages, biofilms develop a three-dimensional structure. It disperses after maturation to create new biofilm colonies regulated by cyclic di-GMP and quorum sensing. It changes depending on nutritional availability, environmental response, and other factors.

The urease enzyme expression of MR/P pilus adheres and colonizes on the catheter. Increased pH initiated crystal formation and led to crystalline biofilm. *Escherichia coli* (UPEC) express type-1 pili, P pilus, or curli to start adherence and colonization. It leads to biofilm-like intracellular communities’ development Cyclic-di-GMP induces the maturation of biofilms through the induced expression of adhesion molecules such as polysaccharine, colanic acid, and cellulose. They act as an EPS for UPEC-mediated biofilm maturation. Finally, the Quorum Sensing Auto inducers induce biofilm’s differential stages through
Figure-1: A schematic representation of the association of uropathogenic bacteria in biofilm formation in CAUTI. Biofilm formation through some major uropathogens. Enterococci spp. (from left) begins biofilm formation through catheterization. Catheterization results in fibrinogen release from uroepithelium and produces proteases that result in the expression of Ebp pilus, Agg, Esp, and Ace adhesin to adhere and colonize on the surface of the catheter. To mature biofilm formation, rhamnopolysaccharides accumulate and act as extracellular polymeric substances. In a mature biofilm, AtlA, GelE, SprE, and SalB are expressed with an increased level of eDNA. In addition, Proteus mirabilis produced urease enzymes to raise urine pH by generating ammonia and CO$_2$ [Source: Figure was prepared by the authors using PowerPoint].

UPEC, P. aeruginosa, and other uropathogens. In the case of P. aeruginosa, it initiates adherence through adhesion molecules and increases the eDNA, Alg, PEL, and PSL production. Alg, PEL, and PSL are the precursor of EPS of P. aeruginosa mediated biofilm. Some virulent factors such as Elastase, ExoS, Rhamnolipids, and Phospholipase induced biofilm formation and developed biofilm on the catheter.

Phage Biology

Phage genetic material could consist of either DNA or RNA genome and encapsulated within a protein capsule or envelope. Phage can therapeutically be used to kill bacteria during an active infection. A controlled lytic cycle is necessary to do so [51, 53].

Usage of Bacteriophages in CAUTIs

As bacteriophage is host-specific [52], it could be a novel strategy to treat CAUTIs, especially the biofilm producers, who can worsen the infected epithelium and catheter tube surface. Bacteriophages can proliferate by lysing the bacterial cells on the surface of biofilms [54]. The “Active penetration” method applies to balance bacterial cell numbers and phage populations [55]. Through the use of three enzymes, phages can affect and degrade biofilms [56–58]. First, the enzymes hydrolyze extracellular polymeric substances in biofilms. Then enzymes destroy the bacterial cell capsule, and enzymes destroy the bacterial cell wall. Finally, the enzyme that can dissolve the biofilm’s EPS induces degradation that contributes to its breakdown and helps phages enter the bacteria encapsulated inside it [56, 57].

Furthermore, phages could encode depolymerization enzymes to degrade EPS further, though research is ongoing to discover this puzzle. However, the degradation of EPS paves the way to more exposure of the bacterial colony to the outer environment. Phages and possibly other treatment strategies synergism with phages, such as antibiotics and chemicals that reduce the bacteria, can attack the colony if EPS is absent or degraded in biofilm through phages’ initial attacks. Phages also attack infected persistent bacteria
cells through the lytic cycle because, in the lysogenic process, it produces prophages rather than phages (Figure-2) [54]. Genetic engineering could prepare the Phage to be compatible with fighting against biofilms, its extracellular properties, and microbial colony. The lytic cycle’s essential genes are constitutive, and the associated genes for advanced progress are inserted in the Phage.

**Bacteriophage Therapy as a Promising CAUTI Therapeutics**

Growing evidence suggests four significant ways to treat bacterial infection through phage therapy. The study observed that natural phage/phage cocktails, genetically engineered phages, phage lytic enzymes, and phages synergism with antibiotics are potent against uropathogenic resistance bacteria strains [52]. Single phages or phage cocktails could help treat the biofilms and assist in further investigation to cope with emerging technologies to fight against biofilms and multidrug antibiotic resistance. In the current research, engineered bacteriophages were prepared to use during infection, producing biofilm-degrading enzymes [59]. A biofilm degrading enzyme coding gene region found in one strain of *Actinobacillus* spp. This gene could be integrated into the Phage through genetic engineering. One strain of *Actinobacillus* spp. incorporates DispersinB (DspB) that expresses biofilm degradation enzyme. DispersinB, a gene encoding DispersinB (β-N-acetyl-glucosaminidase), catalyzes the hydrolysis of the critical adhesion required for the development and integrity of biofilms in all species of *E. coli* and *Staphylococcus* spp. [5, 60] and subsequently damages the bacterial cells in the biofilm and the biofilm matrix. Around 99.9% elimination was achieved after using this mix of bacteriophage-enzyme [59].

Furthermore, the second messenger, c-di-GMP, has been studied in recent years because it is highly

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*Figure-2: Schematic illustration of phage therapy in biofilm degradation. Phage therapy is designed to consider bacteriophage’s capabilities to penetrating the biofilm extracellular polymeric substance (EPS). First, bacteriophage attached (Step 1) the biofilms and expressed depolymerization enzymes to degrade the EPS of biofilms and enter the microbial colony (Step 2). As the number of bacteriophages increases, attachment also increases, and depolymerization occurs. After that, the phages enter the viral genome into the bacterial genome to make phage replication (Step 3). Finally, the phage genome replicates into a bacterial genome and starts assembling (Step 4). Increased phage replication uses the bacterial replication machinery, which leads to lysing releasing new bacteriophages preventing further biofilm formation (Step 5). Also, bacteriophage attacks persisted cells (shows metabolically inactive) to avoid further biofilm formation (Step 5) and the release of numerous mature phages (Step 6). During phage therapy, these cycles of events continue to treat the target of the area of bacterial infection [Source: Figure was prepared by the authors using PowerPoint].*
Pseudomonas, Fig is responsible for most International Journal of One Health, EISSN: 2455-8931 93 is well understood that urothelium-attached sewage water can effectively work against UPEC [64]. It also predicts the low-cost price and kill bacteria individually or synergistically with antibiotics [52, 54]. It also predicts the low-cost price and kill bacteria individually or synergistically with antibiotics [52, 54].

Phage therapy holds a bright potential in treating CAUTI and other bacterial pathogens by removing these restricting factors. However, despite growing evidence of bacteriophage as an effective therapy to get a remedy for CAUTI, some drawbacks and limitations should be considered. As we know, the bacteriophage is host-specific, and it is not easy to prepare a valuable phage to treat CAUTI. In addition, processing the desired bacteriophage is a complex and cumbersome process. Another problem with using bacteriophages is the integrase enzyme that can acquire the antibiotic resistance genes from phage biofilm on urinary catheters by inhibiting the DGC WspR enzyme, which can disperse the P. aeruginosa and Acinetobacter baumannii biofilm. These small molecules include LP 3134, LP 3145, LP 4010, and LP 1062 [5, 62]. In 1919, d’Herelle first successfully treated a few children suffering from severe dysentery in Paris with human phage therapy [63]. Since then, the Pasteur Institute has produced phage preparations against different pathogens (Pseudomonas spp, Staphylococcus spp., E. coli, and Serratia spp.) in France until 1974 [63]. These phages were mainly used against wound infections, UTIs, septicemia, skin infections, otitis media, sinus infections, and osteomyelitis. Until 1979, regular scientific research and reports continued on phage therapy in France [63]. According to several findings, it might be prudent to rethink and re-establish phage therapy. As bacteriophages’ specificity is very high to their respective hosts, the chances of “secondary infections” diminished significantly. This characteristic gives phage therapy superiority over antibiotic treatments.

Bacteriophages often multiply, where they are usually required to lyse the bacteria at the infection site. Still, antibiotics spread around the body and do not focus on the site of infection. Antibiotic therapy’s typical side effects, such as resistant bacteria, allergies that can often also be fatal anaphylactic reactions, and secondary infections, lead to phage therapy over antibiotics. The most significant advantages of phage treatment are that it is environment-friendly and not present in food or animal products. Moreover, one of the major causes of developing MDR is biofilm formation (Figure-2). Phages can penetrate the biofilm and kill bacteria individually or synergistically with antibiotics [52, 54]. It also predicts the low-cost price for maintaining and isolating bacteriophage strains or engineered genetic bacteriophages. This comparison and advantages make “Phage therapy” a novel strategy to treat CAUTI.

**Therapeutic Phage Candidates against CAUTI Bacteria**

A study observed that CAUTI-causing bacterial pathogens had shown a variety of clinical manifestations. Therefore, it is best to counteract these bacterial infections through various in vivo and in vitro experiments with different phages (Table-2) [64–77].

Uropathogenic E. coli is responsible for most CAUTI case reports. A study found that phages from sewage water can effectively work against UPEC [64]. It is well understood that urothelium-attached E. coli can be up to 100 times more antibiotic-tolerant [15]. The T1, T4, and phiX174-like phages were used to reduce loads of UPEC adhered to the epithelium and test their effectiveness under static and shaken conditions after bacterial infection [65]. Among all these phages, T1 Phage was most effective in killing bacteria attached to the urothelium. About 45% reduction was observed after two hours of treatment [15, 65]. This phage was also distinguished by a full lytic spectrum and the capacity to infect numerous antibiotic-resistant strains against clinical E. coli isolates.

A “community-acquired infection” with infectious *K. pneumoniae* initially appeared in Asia mainly in the past two decades, which has since been observed throughout the world [78, 79]. Around 80% of *K. pneumoniae-*induced “nosocomial” infections are linked to MDR strains [63]. In addition, the capacity of bacteriophages to treat mice contaminated with *K. pneumoniae* was reported in one study. “Phage SS.” unique to “K. pneumoniae B5055” is well described, and its clinical application is tested in an observational study of “lobar pneumonia” induced by *K. pneumoniae* [66]. As a result, many clinicians have begun to recommend phage therapy for respiratory diseases [80].

Research has demonstrated that monotherapy alone or in conjunction with antibiotics can be used to treat acute and chronic urologic inflammatory diseases caused by groups of *E. coli*, Staphylococcus spp., and Proteus spp. During the experiments, phage preparations in 46 patients were administered locally and orally. The efficacy of phage therapy was measured, which was found out about 92% (a significant clinical increase was observed) and 84% bacteriologic clearance [81, 82].

In addition to clinical trials, preclinical polyphage therapy experiments included two novel virulent phages (i.e., vB-PmiP-5460 podovirus and vB-PmiM-5461 myovirus) that seem to be very promising in countering CAUTI caused by *P. mirabilis* [67]. Furthermore, based on the dynamic biofilm model simulating CAUTI, a substantial decrease in *P. mirabilis* biofilm formation on catheters was obtained (up to 168 h of catheterization).

**The Problems Need to be Overcome**

Phage therapy holds a bright potential in treating CAUTI and other bacterial pathogens by removing these restricting factors. However, despite growing evidence of bacteriophage as an effective therapy to get a remedy for CAUTI, some drawbacks and limitations should be considered. As we know, the bacteriophage is host-specific, and it is not easy to prepare a valuable phage to treat CAUTI. In addition, processing the desired bacteriophage is a complex and cumbersome process. Another problem with using bacteriophages is the integrase enzyme that can acquire the antibiotic resistance gene from the biofilm-forming bacteria. Through genome modification, the absence of integrase and antibiotic resistance genes from phage...
Table 2: A list of potential phage candidates as therapeutics against CAUTI-causing bacteria.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Type of phage therapy</th>
<th>Name of phage</th>
<th>Order/family of Phage(s)</th>
<th>Animal/model system</th>
<th>Route of administration</th>
<th>Condition</th>
<th>Result</th>
<th>Reference</th>
</tr>
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<tr>
<td><em>E. coli</em></td>
<td>Single phage</td>
<td>T1 phage</td>
<td><em>Siphoviridae</em></td>
<td>Urothelium</td>
<td>UTI</td>
<td></td>
<td>The highest number of antibiotic-resistant pathogenic <em>E. coli</em> reduction</td>
<td>[65]</td>
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<tr>
<td></td>
<td>Phage cocktail</td>
<td>vB_EcoM_ACG-C40 phage+vB_EcoP_ACG-C91 phage+vB_EcoS_ACG-M12 phage</td>
<td><em>Myoviridae</em>, <em>Autographiviridae</em>, and <em>Siphoviridae</em></td>
<td><em>Myoviridae</em></td>
<td><em>In vitro</em></td>
<td>UTI</td>
<td>Lytic activity is almost 80.5% for uropathogenic biofilm-forming <em>E. coli</em></td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>Phage cocktail</td>
<td>T4 phage+KEP 10 phage</td>
<td><em>Myoviridae</em></td>
<td>mice</td>
<td>Peritoneal cavity</td>
<td>UTI</td>
<td>Individually they reduce UPEC respectively 14% and 67%. In cocktails, the reduction of bacteria increases a lot</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>Phage cocktail</td>
<td>Escherichia phage myPSH2311b+Klebsiella phage myPSH1235p+Enterobacter phage myPSH1140</td>
<td><em>Podoviridae</em> and <em>Myoviridae</em></td>
<td><em>In vitro</em></td>
<td>ND</td>
<td>ND</td>
<td>The phage cocktail succeeded in decrease throughout the number of cells of <em>E. coli</em></td>
<td>[69]</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>Single phages</td>
<td>Custom-made lytic phages</td>
<td>N.D</td>
<td>Human</td>
<td>Oral and intrarectal</td>
<td>Obstructive nephrolithiasis, Urinary tract infection</td>
<td>ND</td>
<td>Absence of MDR. and Non-MDR K. pneumoniae in patient's stool and rectal swabs afterward treatments with custom made Phage</td>
</tr>
<tr>
<td></td>
<td>Phage cocktail</td>
<td>Escherichia phage myPSH2311b+Klebsiella phage myPSH1235p+Enterobacter phage myPSH1140</td>
<td><em>Podoviridae</em> and <em>Myoviridae</em></td>
<td><em>In vitro</em></td>
<td>ND</td>
<td>ND</td>
<td>The phage cocktail succeeded in a two-fold decrease in the number of cells of K. pneumoniae</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>ZCKP1</td>
<td><em>Myoviridae</em></td>
<td><em>In vitro</em></td>
<td>ND</td>
<td>ND</td>
<td>Phage decreased its biofilm quality and repetitious phage therapy. The regeneration of K. pneumoniae biofilm extracted from a diabetic patient's foot injury was prevented</td>
<td>[71]</td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>TSK1</td>
<td><em>Siphoviridae</em></td>
<td><em>In vitro</em></td>
<td>ND</td>
<td>ND</td>
<td>Different age biofilm of K. pneumoniae decreased by TSK1 phage by over 95%</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>vB-KpneM-Isf48</td>
<td><em>Myoviridae</em></td>
<td><em>In vitro</em></td>
<td>ND</td>
<td>ND</td>
<td>Phage showed K. pneumoniae specific lytic activity against K. pneumoniae (ATCC 7880) and 38 out of 41 clinical K. pneumoniae isolates</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Phage cocktail</td>
<td>GHK1+GHK 2+GHK3</td>
<td>ND</td>
<td>Murine</td>
<td>Intraperitoneal</td>
<td>Bacteremia</td>
<td>The murine model covered by the Phage cocktail is more potent than single phage therapy Total clearance of pulmonary bacteria on the 5th day after the phage therapy</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>Phage S.S.</td>
<td><em>Podoviridae</em></td>
<td>Mice</td>
<td>Intraperitoneal</td>
<td>Lobar pneumonia</td>
<td></td>
<td>[66]</td>
</tr>
</tbody>
</table>

(Contd...)
<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Type of phage therapy</th>
<th>Name of phage</th>
<th>Order/family of Phage(s)</th>
<th>Animal/model system</th>
<th>Route of administration</th>
<th>Condition</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. mirabilis</em></td>
<td>Phage cocktail</td>
<td>vB_PmiP_5460 phage+vB_PmiM_5461 phage</td>
<td>In vitro</td>
<td>CAUTI</td>
<td>Inhibition of crystalline biofilm formation and eradicated <em>P. mirabilis</em> from the models for up to 168 h</td>
<td>[67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>vB_PmiP_5460</td>
<td>Podoviridae</td>
<td>In vitro</td>
<td>CAUTI</td>
<td>Inhibition of biofilm formation and eradicated <em>P. mirabilis</em> from samples with a host range of 67%</td>
<td>[67]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>vB_PmiM_5461</td>
<td>Myoviridae</td>
<td>In vitro</td>
<td>CAUTI</td>
<td>Prevention of crystalline biofilm formation and eradicated <em>P. mirabilis</em> from the samples with a host range of 100%</td>
<td>[67]</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp. (<em>E. faecalis</em>, <em>E. faecium</em>)</td>
<td>Single phage</td>
<td>vB_EfaS-Zip (Zip)</td>
<td>Podoviridae</td>
<td>In vitro</td>
<td>ND</td>
<td>69% <em>E. faecalis</em> reduced, 23% <em>E. faecium</em> reduced</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>vB_EfaP-Max (Max)</td>
<td>Siphoviridae</td>
<td>In vitro</td>
<td>ND</td>
<td>75% <em>E. faecalis</em> reduced, 15% <em>E. faecium</em> reduced</td>
<td>[75]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single phage</td>
<td>EFDG1</td>
<td>Myoviridae</td>
<td>In vitro</td>
<td>Root canal infections</td>
<td>With a higher dose, it can clear all residue of <em>E. faecalis</em></td>
<td>[76]</td>
<td></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Phage cocktail</td>
<td>M4 Phage</td>
<td>Myoviridae</td>
<td>In vitro</td>
<td>CAUTI</td>
<td>Prevent bacterial colony formation on the catheter</td>
<td>[77]</td>
<td></td>
</tr>
</tbody>
</table>

*E. coli*=*Escherichia coli*, *K. pneumoniae=**Klebsiella pneumoniae*, *P. mirabilis*=*Proteus mirabilis*, *E. faecalis*=*Enterococcus faecalis*, *E. faecium*=*Enterococcus faecium*, *S. saprophyticus*=*Staphylococcus saprophyticus*, *P. aeruginosa*=*Pseudomonas aeruginosa*, CAUTI=Catheter-associated urinary tract infection, UTI=Urinary tract infection
or phage cocktails should be ensured [83]. However, there are also problems associated with the phage particles’ therapeutic formulation and stabilization, and there is a risk that after administration, the immune system will decrease the injected phage [84]. In this case, optimizing the phage particle for each bacteriophage should be phage-centered and performed separately [85].

Bacteriophage makes use of the bacterial cell surface receptor [83]. Thus, receptor mutations may lead to bacterial resistance to bacteriophage. With phage cocktails and a higher initial dose, the growth of bacterial resistance can be mitigated [83]. In addition, lysogenic phages integrate their genetic material into the bacterial genome [83] and exchange genes with antibiotic-resistant bacteria by horizontal transfer of genes. Many more resistant bacteria may also be increased by such transduction. Furthermore, various issues with collecting and administering patents obstruct the success of phage therapy. There are significant issues with phage care since there is no exact legal method for detecting tailored treatments and even pharmacological concerns for phages and phage medications [86, 87].

Other Possible Treatment/Prevention? Drug Target

“Prevention is better than cure” proverb goes for this disease. Most cases of CAUTI can be resolved by the proper management of careful handling urinary complications. There are many proposed treatment mechanisms to cure this disease and prevent CAUTI.

Catheter Coated with Hydrogels or Antibiotics

Hydrogels are water-retaining hydrophilic polymers. This property gives the catheter more surface lubrication, which reduces bacterial adhesion to the catheter’s surface. A study established that a hydrogel layer boosted planktonic cell aggregation, increasing nucleated crystals, producing more rapid catheter blockage than uncoated silicon, and possibly reducing catheter encrustation [88].

Silver alloy-coated hydrogels coated urinary catheters can reduce up to 45% CAUTI [89]. Minocycline-rifampicin-coated catheters have the property to inhibit the biofilm formation of Gram-positive and harmful pathogens, except P. aeruginosa and Candida spp. [90].

Nanoparticles

A nanoparticle is a microscopic particle (<100 nm), which has sparked many scientists’ curiosity because of its vast potential applications. These particles can bind to and penetrate bacterial cells, damage their membranes, and interact with chromosomal D.N.A. [91]. Glass surfaces coated with magnesium fluoride nanoparticles can inhibit biofilm formation by E. coli and S. aureus [91]. Low solubility and prolonged safety resulting from the antibacterial and antibiotic action of yttrium fluoride (YF3) nanoparticles is a suggested component of building a catheter (ID). These particles also have low cytotoxicity [92]. A few experiments on silver nanoparticles have shown the “in vivo” and “in vitro” inhibition of biofilm formation by various bacterial species and the use of determined nanoparticle concentrations [93].

Enzyme Inhibition

Crystalline biofilms are formed by P. mirabilis, which produces urease. Therefore, it would be better to target urease inhibition to prevent biofilm formation. For example, Fluoroamidone significantly prevents urease as it decreases pH in an “in vitro” study [94, 95]. In addition, natural compounds like vanillic acid [96], wild plum juice [97], and germa-γ-lactones [98] showed potent inhibition of bacterial growth and also the formation of crystals in catheters by inhibition of the urease enzyme.

Liposome

Liposomes can eradicate the formation of biofilm. When an antibiotic is encapsulated in a liposome carrier, it cannot interact with the EPS. It also shows the antibiofilm effect and protects against degradation by antibiotic-inactivating enzymes (such as β-lactamases) [99]. Liposomes containing tobramycin and bismuth can destroy P. aeruginosa biofilm [100].

Quorum Sensing Inhibitors

Quorum sensing is a cell-to-cell communication process that allows sharing of information about bacterial cell density to adjust gene expression according to a chemical signal [101]. It coordinates between the gene expression and regulation of Virulence like motility of biofilm formation [102]. QS enables bacteria to restrict gene expression to the high cell densities at which the resulting phenotypes will be most beneficial [103].

Such as low molecular weight, which can reduce QS-related gene expression, is highly specific to QS modulators and must be unable to produce toxic effects against eukaryotic hosts and do not mess with bacteria’s basal metabolic activity and inhibit the progression of resistance.

Antiadhesive Agent

As adherence is necessary to form biofilm formation in UTI and CAUTI, it is best to find a remedy to prevent adherence. In clinical trials, numerous antiadhesive compounds have been evaluated for this purpose. Cranberry extract is well studied in the present day [5]. It inhibits adherence effects of UPEC through the A-type proanthocyanidin. FimH adhesin is another crucial player in biofilm formations inhabited by mannosidase, as proved in a recent study [1]. The study found an association between cotrimoxazole (antimicrobial agent) and mannosides. Salicylates, common aspirin ingredients, reduce type 1 pili and
OmpA expression, resulting in decreased biofilm formation and extracellular matrix, respectively [104].

Conclusion

UTI is a reasonably frequent ailment affecting people of all ages and genders worldwide. Several microbial agents have been identified as potential UTI and CAUTI causes. The most common UTI-causing organisms and their pathogenesis were examined in this review, as well as the involvement of the catheter in the development of bacterial biofilm-associated UTI and treatment complications due to the presence of MDR bacteria. The current review has also demonstrated a proposed model of phase therapy against biofilm-linked UTI-causing bacteria. However, extensive research is required to formulate an effective phase particle to treat CAUTI because of its host specificity attributes. In this review, we attempted to assemble many features of CAUTI that would suggest new compounds with antibiofilm capabilities for researchers to identify to prevent or eliminate the spread of biofilm-generating bacteria. Based on this knowledge, our study team has already begun plotting an original investigation on employing nanotechnology against various bacterial and viral disorders. Scheming and implementing the virus-like particle as a contender for use instead of synthetic drugs against drug-resistant bacteria, particularly MDR strains, could be a new challenge for us.

Authors’ Contributions

AS and MA: Designed and planned the study. AS, MFRS, HA, and ARM: Drafted the manuscript. TA, MA, and MRM: Revised the manuscript for necessary changes in format, grammar, and English standards. AS and MFRS: Prepared the figures and edited the manuscript. All authors have read and approved the final version of the manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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