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Efficacy of anti-microbial catheters in preventing catheter associated urinary tract infections in hospitalized patients: A review on recent updates

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ABSTRACT

Catheter-associated urinary tract infections (CAUTIs) are the common hospital-associated infections (HAIs), which can be prevented by practicing necessary precautions and by using antimicrobial urinary catheters (UCs). The efficacy of antimicrobial UCs against standard catheters for averting CAUTIs is poorly studied. The objective of the review is to analyze the efficacy of various types of antimicrobial UCs used in hospitalized patients in preventing CAUTIs. The major antimicrobial UCs are silver and antibiotic catheters, in contrast, few antimicrobial catheters include antimicrobial peptides, bactericidal enzymes, bacteriophages, and many are under clinical evaluation. The review concludes that even though many antimicrobial methods are available to prevent CAUTIs, the incidence rate is still high. Antibiotic resistance, leaching of catheter materials which may cause side effects and additional costs are the major challenges for the UCs. Further research is warranted and should focus on cost-effective and ideal antimicrobial UCs, in which the microorganisms cannot form biofilms or develop resistance.

Contents

Introduction

With the advent of implantable medical devices, the patient care quality has improved to a greater extent. Among them, Urinary Catheters (UCs) are used in almost 15–25% of hospitalized patients. UCs are used in both male and female patients to manage urinary drainage, urinary retention or urinary incontinence, for those who have undergone any surgeries or have problems with mobility [1,2].

Due to their malleability, various materials are used for making UCs such as polyvinyl chloride (PVC), latex rubber, polyurethane, and silicone. The desirable characteristics of a material to be used for manufacturing UCs are having high tensile strength, pliability, resistant to corrosion and chemicals, etc. [3]. Though latex has been

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commonly used in UCs, later it was observed that it has poor chemical and ultraviolet resistance, exhibits allergic reactions in patients and rough surface and may lead to the formation of biofilms [4]. Silicone is the suitable material of choice for UCs as it fulfills most of the requirements with a fewer disadvantage when compared to other materials [5].

UCs are of different types, which are classified mainly depending upon the duration of use in patients. Single-use external catheters can be placed outside the body and replaced daily. Short term catheters are inserted several times a day and used only for a short period (less than 28 days) whereas, long term catheters are used for more than 28 days. An indwelling catheter or Foley catheter is a catheter which can be inserted into the bladder and retained for a long time ranging from few weeks to months [1–5].

Each hospital follows standard protocols for the insertion, maintenance, and removal of these catheters to prevent microbial contamination which includes maintaining hygiene practices like hand washing, use of sterile gloves, intermittent catheterization, no-touch insertion techniques, evaluation of urinary cultures at regular intervals and use of proper catheter materials [1]. Despite following hygiene procedures, UCs are reported to be highly susceptible to - the formation of biofilms, leading to catheter associated-urinary tract infections (CAUTIs).

According to the Centers for Disease Control and Prevention, there are three criteria to define CAUTI in a patient as follows: (1) CAUTI is a UTI where an indwelling urinary catheter was in place for more than two days on the date of event, with day of device placement being day one, and an indwelling UC was in place on the date of event or the day before. If an indwelling urinary catheter was in place for more than 2 consecutive days in an inpatient location and then removed, the date of event for the UTI must be the day of device discontinuation or the next day for the UTI to be catheter-associated. (2) Patient has at least one of the following signs or symptoms, i.e., fever with temperature more than 38.0 °C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, dysuria. (3) Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of more than 10^5 CFU/ml. CAUTIs are the most common nosocomial infections which account for up to 75–80% of all the hospital-associated infections (HAIs). CAUTIs are reported in 80% of patients with indwelling UCs at a rate of 3–10% per day during catheterization. Infection is observed in 10–50% of patients with short-term catheterization whereas, if left untreated, it can lead to serious complications such as pyelonephritis, bacteremia, septicemia, and sepsis which accounts for significant morbidity and mortality associated with CAUTIs [1,7–10]. Bacterial species such as *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus species*, *Proteaus mirabilis*, *Klebsiella pneumoniae*, *Proteus vulgaris, Enterococcal species* and fungal species such as *Candida albicans* can cause CAUTIs (Table 1) [9,10].

Table 1
Most common pathogens causing CAUTIs.

Common pathogens causing CAUTIs
Pseudomonas aeruginosa,
Staphylococcus aureus,
Staphylococcus epidermidis,
Klebsiella pneumoniae,
Proteus mirabilis,
Proteus vulgaris,
Escherichia coli,
Citrobacter freundii,
Providentia rettgeri,
Enterobacter cloacae,
Enterobacter aerogenes,
Enterococcus faecalis,
Enterococcus faeciu,

To prevent the growth of pathogenic microbes in UCs an antimicrobial substance can be coated or incorporated into such materials (Fig. 1) which may be bactericidal or bacteriostatic or act as antifouling agents [6,11]. This review is focused on the recent updates regarding the efficacy of antimicrobial UCs in the prevention of CAUTIs in hospitalized patients.

Antimicrobial agents used in urinary catheters

There are different types of antimicrobial agents which inhibit the colonization of the catheters with pathogenic microbes and prevent CAUTIs. Each type of antimicrobial agent acts in various ways to prevent CAUTIs: (1) by slowly releasing antimicrobial agents; (2) by modifying the surface of catheters to prevent adherence of microbes; (3) contact killing; (4) disrupting the biofilms formed on catheters (Fig. 2) and (5) by using bacterial biofilms to prevent pathogen colonization [6].

Some of the antimicrobial agents have been tested and have been validated by clinical trials and many are still under clinical trials and developmental stage. Silver or antibiotic-coated catheters are the most commonly used antimicrobial catheters which are studied widely in clinical trials and are reported to have reduced CAUTIs [1]. Many studies report the efficacy, advantages and disadvantages regarding the use of silver and antibiotic UCs and hence these two types of UCs are discussed in detail, in this review.

Antimicrobial agents such as antiseptics, biocidal enzymes, bacteriophages, etc. are used in UCs to prevent CAUTIs, which are under clinical trials (Table 2). Antiseptics like chlorhexidine and triclosan have antifungal and antibacterial properties (Table 3). Short strands of peptides with antimicrobial action called antimicrobial peptides (AMPs) are considered to be potent antimicrobial agents due to its

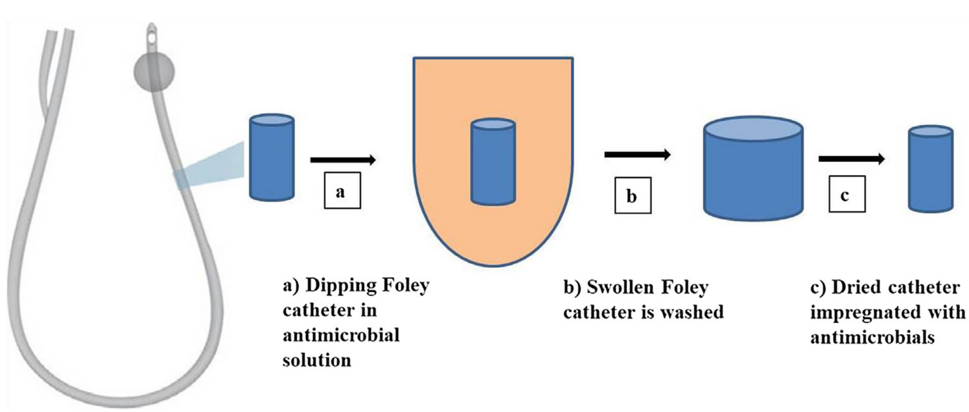


Fig. 1. Incorporation of antimicrobials to Foley catheters.

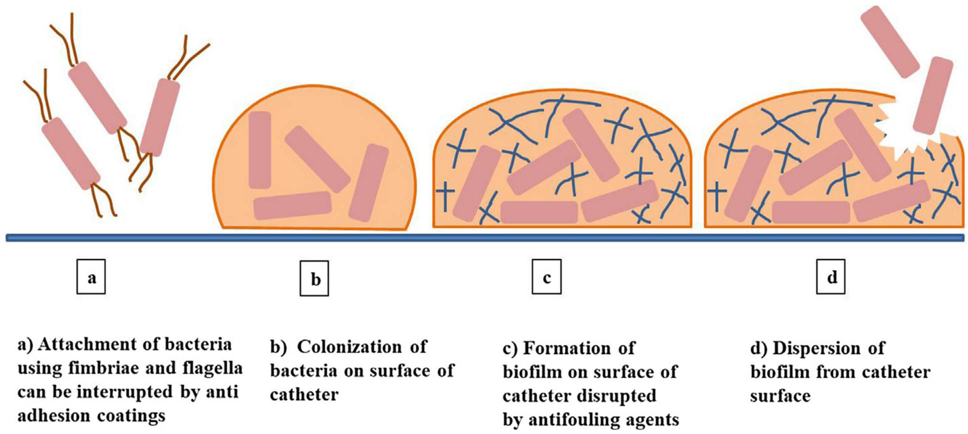


Fig. 2. Disruption of bacterial colonization on UC surface by antimicrobial action.

Table 2
Some of the antimicrobials which are under clinical trials for use in catheters.

Antimicrobial used	Mode of action
Antimicrobial peptides	Short strands of aminoacids with antimicrobial activity which act on the cytoplasmic membrane, inhibit synthesis of DNA, RNA or protein or by immunomodulation
Bacteriophages	Viruses that can invade and destroy bacteria
Enzymes	Hydrolytic enzymes which act on exopolysaccharides disrupt the formation of biofilms. Quorum quenching enzymes prevent quorum sensing
Nitric oxide	Nitrosation of amines, thiols, lipid peroxidation and DNA cleavage
Polyzwitter ions	Polyzwitter ions have both cationic and anionic groups with a neutral backbone, which resist bacterial adhesion by repulsion

broad-spectrum activity with a very low possibility of developing any resistance by microbes [12]. Bacteriophages, the viruses which are natural predators of bacteria can disrupt various metabolic pathways in bacteria. Due to high specificity for target pathogens and low cytotoxicity for humans, these viruses are under trials for effective antimicrobial coatings on UCs [13,14]. Pathogen-specific antimicrobial enzymes can be incorporated into the coatings of UC, which will not affect the normal microflora and thus reduce the possibility of developing any resistance [1].

Silver

Silver, one of the commonly used antimicrobial agents in medical devices to prevent microbial invasion, is approved by the Food and Drug Administration (FDA) to be used in UCs. Bardex® IC and Dover™ are the two most commonly used and studied silver Foley catheters. Silver is coated onto both external and internal surfaces of the catheters, used as an alloy along with gold or platinum, or with nanoparticles and polymers.

Several clinical trials have been conducted to evaluate the effectiveness of silver coated catheters in preventing CAUTIs. A study by Nandkumar et al developed an easy and cost effective method of coating silver oxide onto latex catheters [15], and the efficacy against bacteria isolated from the Foley catheters of patients with CAUTI was tested. Interestingly, the study showed an active inhibition of pathogens such as *E. coli*, *P. aeruginosa* and *P. mirabilis* in the presence of silver oxide which were resistant to other antibiotics. These silver oxide-coated catheters were effective against both gram positive and gram negative organisms, retained its physical properties and were noncytotoxic [15]. A study by Stenzelius

Table 3
Chemical structure of antiseptics used in UCs.

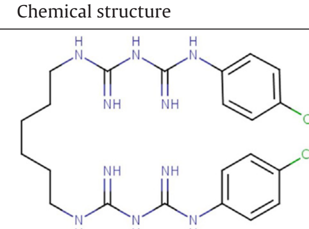
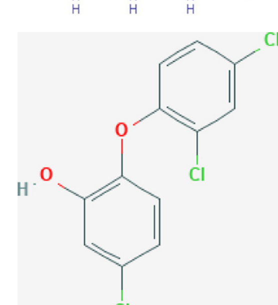
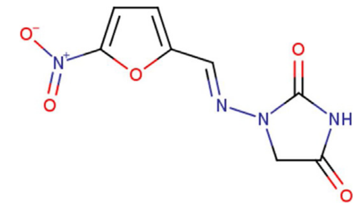
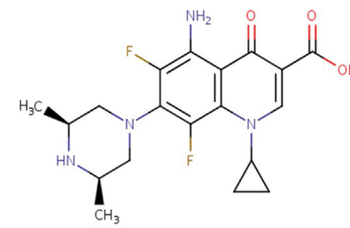
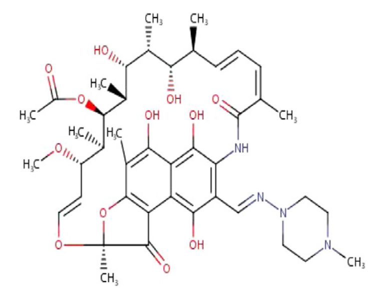
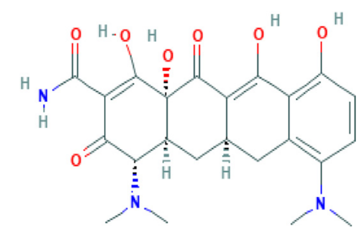
Antiseptic	International union of pure and applied chemistry name	Chemical structure
Chlorhexidine	(1E)-2-[6-[[amino-[(E)-[amino-(4-chloroanilino)methylidene]amino]methylidene]amino]hexyl]-1-[amino-(4-chloroanilino)methylidene]guanidine	
Triclosan	5-chloro-2-(2,4-dichlorophenoxy)phenol	

Table 4
Chemical structure and IUPAC names of some antibiotics used in UCs.

Antibiotics	IUPAC name	Chemical structure
Nitrofural	[(E)-(5-nitrofuran-2-yl)methylideneamino]urea	
Sparfloxacin	5-Amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid	
Rifampin	[(7S,9E,11S,12R,13S,14R,15R,16R,17S,18S,19E,21Z)-2,15,17,27,29-pentahydroxy-11-methoxy-3,7,12,14,16,18,22-heptamethyl-26-[(E)-(4-methylpiperazin-1-yl)iminomethyl]-6,23-dioxo-8,30-dioxa-24-azatetracyclo[23.3.1.14,7.05,28]triaconta-1(29),2,4,9,19,21,25,27-octaen-13-yl] acetate	
Minocycline	(4S,4aS,5aR,12aR)-4,7-bis(dimethylamino)-1,10,11,12a-tetrahydroxy-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide	

et al compared the incidence rate of bacteriuria in silver-coated catheters to standard catheters in orthopedic surgery patients. Interestingly, CAUTIs risk was reduced by 3.7-fold with the use of silver alloy coated short term catheterization [16]. Another report by Bonfill et al showed that a relative reduction of 35% in CAUTI incidence with the use of silver alloy coated (BIP Foley catheter) silicone catheters when compared to standard silicone catheters, in long time catheterized patients [17]. Lederer et al reported a 47% reduction in the occurrence of symptomatic CAUTIs by silver alloy hydrogel (SAH) catheters [18]. In a non-randomized prospective study by Chung et al found that incidence of CAUTI per 1000 catheter-days were reported to be 6.4 for SAH catheters whereas the incidence rate of CAUTI for conventional latex Foley catheters without hydrogel was 9.4. The incidence of CAUTI was reduced by 31% in SAH patients. Although the results were not statistically significant, CAUTI was reduced in high-risk patient groups such as females and long term users [19].

A comparative evaluation of ionic and elemental silver additive were evaluated by using polyamide 11 as a matrix (PA11/Ag) for their antimicrobial properties and ion release properties in catheters, by Thokala et al. Evaluation of surface antimicrobial properties of PA 11/Ag against *E. coli* ATCC 8739 strain indicated a reduction in the bacterial growth within 24 h. The rates in which ions are released showed that elemental silver composites are suitable for long-term catheterization. Ionic silver composites are more suitable for shorter-term catheterization to prevent microbial growth on the surface with a burst release of silver ions within 48 h [20].

However, there are few studies which contradict the above findings which should be analyzed in detail for further applications. In a prospective study, SAH catheters were compared with standard silicone catheters in which the incidence rate of UTIs in the silver group were 14.3 and 16.2 in the non-silver group. Although low UTI rates have observed in the silver group, the difference was not significant when compared to the non-silver group. In conclusion, silver impregnated Foley catheters were not effective in preventing UTIs [21]. Similarly, a study by Desai et al reported that silver coated silicone catheters are lesser effective in preventing CAUTIs [22]

In order to increase the antimicrobial properties of silver, a novel form of silver coatings have been developed such as silver nanoparticles (Ag NPs). Ag NPs have a particle size of less than 100 nm and a large surface to volume ratio. The mechanism of antimicrobial action of Ag NPs is by releasing antibacterial silver ion, which disrupts cell membrane and increases the membrane permeability causing cell death [6,23,24]. A study by Aflori et al. prepared a novel coating in which silicon-coated latex catheters were plasma treated followed by a wet treatment of the catheters in sodium hydroxide and silver nitrate solution. These catheters gave the best results in the antibiograms for biofilm formation and bacterial adhesion [25].

In addition, studies have indicated that silver can be combined with other active materials increase the antimicrobial activity

Table 5
Studies regarding effectiveness of various UCs to prevent CAUTIs in patients.

Population	Intervention	Comparison	Outcome	Reference
RCT (n = 7102)	Silver alloy (Latex) vs. Nitrofural (Silicone) vs. Standard (PTFE)- (latex) A SAH-coated latex catheter (2097) B Nitrofurazone-impregnated silicon catheter(2153) C Polytetrafluoroethylene- (PTFE) coated latex catheter (2144)	A 263/2097 B 228/2153 C 271/2144	No effect on the rate of CAUTI	Pickard et al. [29]
RCT (n = 212)	A Nitrofurazone-coated catheter (104) B Standard silicone catheter (102)	A 9.1% B 24.7%	Incidence of CAUTI was reduced in nitrofurazone coated catheter	Stensballe et al. [34]
RCT (n = 509)	A Noble metal alloy-coated latex catheter (217) B Standard silicone Foley catheter (222)	A 1.5% B 5.5%	Noble metal alloy coated catheters reduced the risk of CAUTI	Stenzelius et al. [16]
RCT (n = 742)	A Silver alloy coated catheter (371) B Standard catheter (371)	–	35% reduction in the relative incidence of CAUTI	Bonfill et al. [17]
Cohort (n = 853)	A Standard catheter (453) B SAH catheter (400)	–	47% reduction in CAUTI in silver alloy/hydrogel coated catheter	Lederer et al. [18]
Prospective (n = 306)	A Conventional Foley catheter (187) B SAH catheter (36)	CAUTI episodes in 1000 days A = 9.4 B = 6.4	31% reduction in incidence of CAUTI when SAH was used	Chung et al., 2017 [19]
Prospective (n = 3036)	A Silver catheter (1165) B Non silver catheter (1871)	UTI per 1000 days A = 14.29 B = 16.15	Silicon-based silver impregnated Foley catheters not effective	Srinivasan et al. [21]
(n = 27,548)	A Standard catheter (15,627) B Antimicrobial catheter (11,921)	A = 1378 B = 994	No significant reduction in incidence of CAUTI in antimicrobial catheters	Muramatzu et al. [35]

(RCT- Randomised Controlled Trial; SAH- Silver alloy and hydrogel coated catheter; PTFE- polytetrafluoroethylene).

[28], which includes phosphorylcholines with silver nanoparticles [26], silver coating releasing hydroxyapatite materials [27] and exopolysaccharide functionalized silver glycol nanoparticles.

Advantages and disadvantages of silver impregnated catheters

Due to the broad-spectrum antimicrobial activity, ease of manufacture, lower cost, and lesser side effects when compared to those with nitrofural, silver-coated catheters will continue to be considered for preventing CAUTIs. One of the disadvantages of silver impregnated UCs are that they lose antimicrobial activity over long periods and not always suitable for long-term catheterization and exhibit slight cytotoxicity when compared to antibiotic catheters. But the advent of silver nanoclusters with sizes less than 2 nm may be promising in the future due to its high antimicrobial activity. The other advantage of silver impregnated catheter compared to nitrofurazone was that it showed more comfort during insertion of the catheter, the period the catheter is in place removal, and three days post catheter removal [29].

Antibiotic coatings

Antibiotics are low molecular weight compounds isolated from microorganisms which have antimicrobial or bacteriostatic properties. These antibiotics once impregnated onto the catheters have a direct action on the pathogens. They inhibit biofilm formation by slow and controlled release of antibiotics to the site of colonization. Antibiotics used in UCs are nitrofurazone, minocycline, rifampin, gentamicin, norfloxacin, sparfloxacin, and vancomycin (Table 4) [30–32].

Nitrofurazone acts against both gram-positive and negative bacteria by inhibiting several bacterial enzymes involved in the aerobic and anaerobic degradation of glucose and pyruvate. Catheter-associated bacteriuria and fungiuria (CABF) occurred less frequently in the nitrofurazone catheter group (9.1%) than in the silicone catheter group (24.7%). The incidence rate of CAUTI was reported to be 13.8 in nitrofurazone group against 38.6 in the standard catheter group. Nitrofurazone catheters led to delayed onset of CABF and less use of antibiotic treatment [34].

In a study conducted by Johnson et al. 11 different pathogenic isolates were compared for the efficacy of nitrofurazone catheters and silver alloy catheters. All-silicone catheters were used as control for nitrofurazone catheters and latex-hydrogel catheters as control for silver alloy catheters. Viable counts were significantly lower for the nitrofurazone catheters relative to its control, but this was not the case for the silver alloy-coated catheter when compared to its control. Absolute viable counts were significantly lower for the nitrofurazone catheter when compared to a silver alloy-coated catheter. In this assessment of antimicrobial catheters for inhibition of pathogenic microbes, a nitrofurazone-coated catheter was reported to be better than the silver alloy-coated catheter suggesting the use of nitrofurazone-coated catheters for preventing CABF [30]. Kowalczuk et al. reported that if indwelling catheters used for long term catheterization were incorporated with the antibiotic sparfloxacin, they exhibited potent action against biofilm formation and bacteria, which in turn inhibited invasion and infection by *E. coli* and *S. aureus* [33].

A comparative study was conducted to evaluate the potential of different urinary catheters on biofilms of clinical isolates and laboratory strains by Kart et al. [9]. The results indicated that the nitrofurazone-impregnated silicone catheter fully inhibited the growth of *S. epidermidis* and *P. aeruginosa* and biofilms. The hydrophilic-coated catheter was significantly more effective for *P. aeruginosa* than the silico-latex and silicone only catheters. Meanwhile, a silver-coated catheter was significantly more effective than the hydrophilic-coated catheter against *S. epidermidis*. *E.coli* and *E. faecalis* formed significantly lower biofilms on the nitrofurazone-impregnated silicone catheter when compared to catheters without nitrofurazone coating. Prolonged antimicrobial duration was exhibited by nitrofurazone-impregnated silicone catheter against the laboratory strains that were tested [9,34].

Fisher et al. evaluated the duration of activity of different antimicrobial combination and their concentrations, distribution on catheter and effect of processing on mechanical properties, in a novel long-term antimicrobial catheter. Rifampicin, sparfloxacin, and triclosan, were the antimicrobials chosen for their action against CAUTI pathogens. These catheters coated with antimicrobials were able to prevent colonization by common uropathogens *P. mirabilis, E. coli and S. aureus* for 7–12 weeks whereas other commercial antimicrobial catheters were active only for 1–3 days. Different combinations of antimicrobials reduced antibiotic resistance and surface analysis revealed that this procedure does not have any adverse effects on the mechanical properties of the catheter. These factors make this antimicrobials coating procedure very useful for patients using long term catheters for urinary drainage [31]. Association between the use of antimicrobials urinary catheters and the incidence rate of CAUTI was also investigated in cerebral infarction patients by Muramatsu et al. Antimicrobial catheters used were antimicrobial-mixed latex or antimicrobial-mixed silicon catheters. CAUTI was reported in 8.8% of patients using standard catheters and 8.3% of patients using antimicrobial catheters. Though the incidence rate of CAUTI in the antimicrobial catheter group was 2.1 per 1000 patient days, there was no statistically significant difference when compared to standard catheters. There was a reduction of CAUTI when antimicrobial catheters were used in diabetic patients [35]. However a study conducted by Pickard et al. indicated that silver alloy-coated catheters were not effective in inhibiting CAUTIs and though there was a reduction in CAUTIs in nitrofural-impregnated catheters, it was not significant (Table 5) [29,36] A long term study conducted in UK on urinary catheter samples identified considerable change in antibiotic resistance in the bacterial species causing CAUTI [1,37].

Advantages and disadvantages of antibiotic coated catheters

The major concern regarding the use of antibiotics in UCs is the development of resistance of microbes against these antibiotics [1,37]. Use of bactericidal enzymes or a combination of different antibiotics could be a solution for antibiotic resistance which requires further clinical trials. Nitrofurazone is reported to cause discomfort in most of the patients which is a major drawback considering its common use in UCs. [38].

Conclusion

CAUTIs are among the leading causes of morbidity and mortality among HAIs. Formation of biofilms, encrustation and the emergence of antibiotic resistance of microorganisms are the major challenges in developing new urinary catheters. Incorporation of different approaches to address these concerns is required in the future. It can be implemented by using different antimicrobial agents which will either inhibit the growth or kill the pathogens. Cytotoxicity of these antimicrobial agents should be studied in vitro and in vivo, in order to prevent any side effects to patients. Coating the UCs with antifouling agents will prevent adhesion, aggregation of pathogens and formation of biofilms on the catheter surfaces. While developing new types of UCs or improving the existing ones, comfort and welfare of the patient should be given priority along with other factors such as cost and drug resistance issues. However, due to increased rate of infections associated with catheterization, more research and trials are required to reduce the incidence of CAUTIs.

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Competing interests

None declared.

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