REVIEW
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Biofilm in indwelling urinary catheter and patient safety: a literature review

Biofilme em cateter vesical de demora e a segurança do paciente: uma revisão da literatura

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ABSTRACT

Introduction: Urinary tract infection associated with indwelling urinary catheter accounts for about 40.0% of health care-related infection. **Objective:** To identify, based on literature review, the factors associated with biofilm formation in an indwelling urinary catheter. **Method:** An integrative review conducted in the databases: Medline, Lilacs, IBECS, PubMed and Portal Capes, using the descriptors "urinary tract infections", "urinary catheters" and "biofilm", with articles published in full between 2009 and 2016 in English, Spanish or Portuguese. **Results:** Eight articles were selected, four systematic reviews and four observational studies. A biofilm on an indwelling urinary catheter is formed by the fixation that is initiated by the deposition of urine on the surface of the catheter. The factors associated with biofilm formation on an indwelling urinary catheter were type of microorganisms (87.5%) (presence of flagella, motility and production of urease), structural conformation (37.5%) in latex (irregular hydrophobic and hydrophilic surfaces) that allow the adhesion and colonization by several microorganisms, and the female sex (12.5%). **Conclusion:** This review identified the factors that were associated with biofilm formation in an indwelling urinary catheter and contributes to the proposal of effective prevention measures focused on patient safety.

KEYWORDS: Urinary Tract Infections; Urinary Catheters; Biofilm

RESUMO

Introdução: A infecção do trato urinário associada a cateter vesical de demora (ITU-CVD) representa cerca de 40,0% das infecções relacionadas à assistência à saúde (IRAS). **Objetivo:** Identificar através da literatura os principais fatores associados à formação do biofilme em cateter vesical de demora (CVD). **Método:** Revisão nas bases de dados: Lilacs, Ibecs PubMed e Portal Capes, utilizando os descritores: "infecção do trato urinário"; "cateteres urinários" e "biofilme" de artigos publicados na íntegra entre 2009 e 2016, nos idiomas inglês, espanhol ou português. **Resultados:** Foram selecionados oito artigos, sendo quatro revisões sistemáticas e quatro estudos observacionais. Os biofilmes nos CVD são formados pela fixação de patógenos que se inicia pela deposição de urina na superfície do cateter. Os fatores associados à formação do biofilme no CVD foram: tipo de microrganismos (87,5%), presença de flagelos, motilidade e produção de urease, conformação estrutural (37,5%) em látex (superfícies irregulares hidrofóbicas e hidrofílicas) que permitem a adesão e colonização por vários microrganismos, e o sexo feminino (12,5%). **Conclusões:** a presente revisão identificou os fatores associados à formação do biofilme no CVD e assim contribuiu para a proposição de medidas eficazes na prevenção com foco na segurança do paciente.

PALAVRAS-CHAVE: Infecção do Trato Urinário; Cateteres Urinários; Biofilme

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INTRODUCTION

Urinary tract infections associated with indwelling urinary catheters (UTI-IUC) account for approximately 40% of healthcare associated infections (HAI) and virtually all cases of nosocomial UTI are related to the use of urinary catheters (UC)[1].

The incidence of bacteriuria, presence of bacteria in urine, in catheterized patients is proportional to the catheterization time. The daily risk ranges from 3% to 10% and after 30 days it reaches 100%. After the insertion of the IUC, bacteria that colonize the urethral meatus adhere to the inner and/or outer surface of the catheter and can initiate the formation of biofilm, a complex of organic material formed by microorganisms that grow in organized cell colonies surrounded by a matrix composed mainly of microbial exopolysaccharides (EPS), nucleic acids, proteins and lipids. The biofilm enhances the adhesion of microorganisms to the catheter surface in a way that it becomes difficult to remove it. And the reverse can also occur, the surface of the catheter enhances the adhesion of the bacteria and thus the formation of biofilm, causing the UTI-IUC[1,2].

The biofilm is the main risk factor for HAIs and it is estimated that approximately 65 to 80% of infections related to the invasive devices are associated with its presence. The time required to form a biofilm in a urinary catheter depends on the microbial association, device and material type[3,4,5]. Biofilms in urinary catheters are considered an important risk factor for UTI-IUC, which leads to prolonged treatments, high treatment costs and mortality rates[6].

Biofilm formation is directly related with the microorganisms' ability to colonize the catheter. In general, the microorganisms most commonly found in urinary catheter biofilms are *Escherichia coli*, *Enterococcus* sp, *Proteus mirabilis* and *Klebsiella pneumoniae*[5]. These bacteria adhere to the catheter surface and get surrounded by the EPS layer. This situation makes them highly resistant to antibiotics, increases the possibility of horizontal gene transfer and their protection against host defense mechanisms and antiseptics. This situation leads to severe clinical implications[7,8,9].

Therefore, biofilms play an important role in the pathogenesis of UTI-IUCs. Given the relevance of this subject, we expect that the results help understand the practices that can minimize/eliminate the possible factors associated with biofilm formation in urinary catheters. In view of the above, the aim of this study was to search for evidence in the literature about the factors associated with biofilm formation in IUC.

METHODS

We made literature review based on the following steps: theme identification and formulation of the research question, elaboration of criteria to include or exclude papers, construction of a mimic diagram for data collection of the selected papers, evaluation and analysis of papers, interpretation and discussion of the results and presentation of this review.

The papers were surveyed in the Brazilian Virtual Health Library (VHL) databases: Latin American Literature on Health Sciences (Lilacs) and Spanish Bibliographic Index of Health Sciences (Ibecs); in addition to the U.S. National Library of Medicine of the National Institute of Health (PubMed) and *Portal Capes* website databases. For the selection of papers, we consulted the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). We identified and used the controlled descriptors in Portuguese, English and Spanish: urinary tract infection, urinary catheters and biofilm. We adopted the following search strategy: "Mesh:c01.539.895" OR "Urinary Tract Infections" OR "Infecciones Urinarias" OR "Infecciones Urinarias"; AND "Mesh:e07.132.625" OR "Cateteres Urinários" OR "Urinary Catheters" OR "Urinary Catheter" OR "Cateter Urinário" OR "Catéteres Urinarios" OR "Sonda Vesical de Demora"; AND biofilm*.

Inclusion criteria were: papers in English, Portuguese and Spanish, published in the last nine years (2009 to 2017), considering the publication date of the Guideline for Prevention of Catheter Associated Urinary Tract Infections[10].

We searched for the papers from October 2016 to February 2017 and found 943 papers, 156 of which were selected and, after comparative reading, 51 were excluded because they were duplicated, adding up to 105 papers for the next step. In this step, we read the 105 papers entirely and found that 97 did not meet the previously determined criteria or the guiding question, and the final sample consisted of eight papers. Figure 1 illustrates the selection process of papers in this review.

For data collection we prepared a mimic diagram adapted for this study, which included the following items: identification data of the original paper (authors, journal and year), objectives, key results and conclusions and level of scientific evidence of the study.

For determination of the level of evidence of the studies, they were hierarchized according to a reliability and validity evaluation, which considered the methodological approach, the experimental design and the quality of the results. For this evaluation, we considered: level I - evidence obtained from the result of a systematic review or meta-analysis of all controlled and randomized clinical trials or from guidelines based on systematic reviews of controlled clinical trials; level II - evidence obtained from at least one controlled, randomized and well designed clinical trial; level III - evidence from a well designed and controlled but not randomized study; level IV - evidence from case-control or cohort studies; level V - evidence from a systematic review of qualitative and descriptive studies; level VI - evidence from a single descriptive or qualitative study;

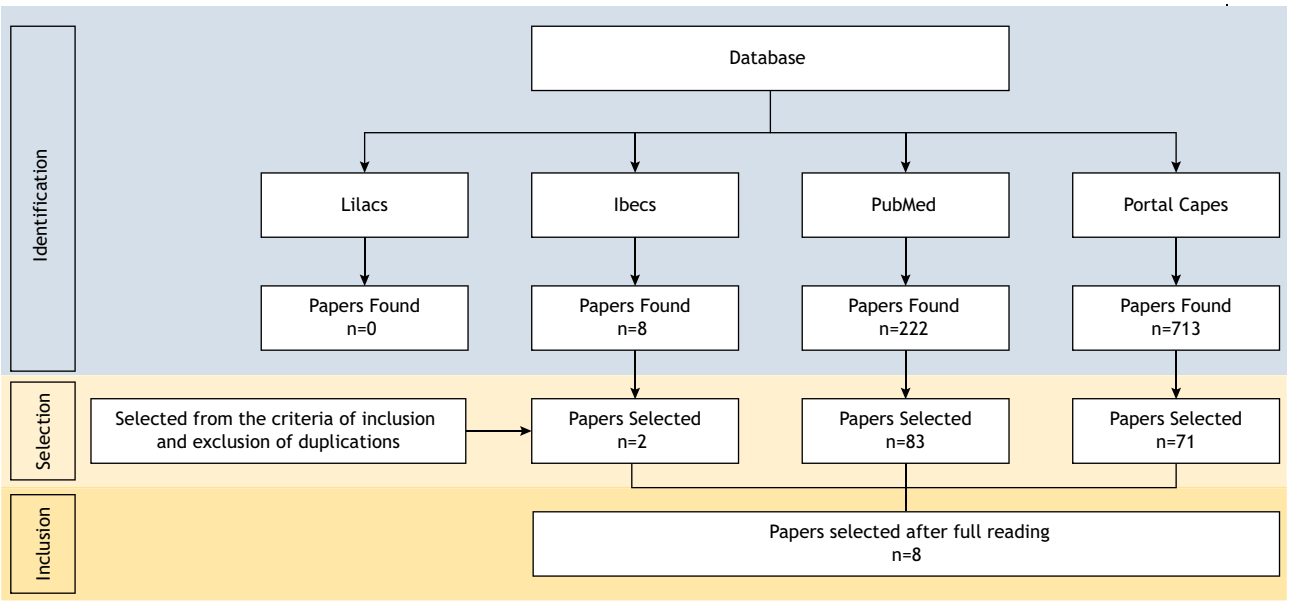

Figure 1. Diagram of the analysis and selection process of the papers included in this review. Lilacs: Latin American Literature in Health Sciences; Ibecs: Spanish Bibliographic Index of Health Sciences; PubMed: U.S. National Library of Medicine of the National Institute of Health.

Level 7 - evidence from the opinion of authorities and/or specialists/experts commission reports[11].

After full reading and data extraction from the selected papers, we presented the results in charts and graphs with the most relevant factors associated to the biofilm formation in IUCs.

RESULTS

The sample of this review was composed of eight studies, published between 2009 and 2016, three (37.5%) of which in 2014. Of these publications, seven (87.5%) were in English, one (12.5%) in Spanish and none in Portuguese. Among the journals, the main ones came from PubMed, adding up to six (75%) studies, one came from Ibecs (12.5%) and one (12.5%) from Portal Capes database.

The main factors associated with biofilm formation in IUCs identified in the studies were: microorganism type (87.5%); catheterization time (62.5%), IUC structural conformation (37.5%) and being female (12.5%) (Table 1).

To enable the understanding of the findings, the studies included in this review were grouped according to risk factors and level of evidence in table 2.

Regarding the level of evidence, we observed that half of the studies were classified as level V, that is, evidence from a systematic review of qualitative and descriptive studies. Regarding the publications in the analyzed period, it is evident that the production of papers related to this subject did not grow, which is a challenge for the prevention of UTI-IUC, since biofilm formation is the main risk factor for these infections (Figure 2).

DISCUSSION

The factors associated with IUC biofilm formation identified in this study are related to microorganisms, structural conformation of the IUC and the intrinsic conditions of the patient. The arrangements of these factors occur from the insertion of the IUC and subsequent growth of the biofilm, which rapidly occupies the entire surface[9,16].

Factors related to the microorganism

IUC biofilms are formed by Gram-positive and/or Gram-negative bacteria and fungi through the fixation, that starts with urine deposition in the catheter surface[15,16]. In addition, the motility and presence of flagella in the uropathogens enhance the adhesion required for biofilm formation[3,17]. Some studies identified significant biofilm formation in UTI-IUC in samples of *E. coli* (60-80%), *Klebsiella* sp (16-21%), *Staphylococcus* coagulase negative (3-6%), *P. mirabilis* (6%), *Pseudomonas aeruginosa* (2-4%), *Acinetobacter* spp (1-2%) and *Enterococcus* (2%)[13,14,19].

Another important aspect is the ability of the microorganisms to produce urease, which contributes to the formation of crystalline biofilm in the IUC and its obstruction[5]. *P. mirabilis*, the most common pathogen in chronic catheterization, is responsible for most obstructions[5,9]. The urease produced by this microorganism hydrolyzes urea six to ten times faster than other species[3,5,9] and the released ammonia increases urine pH and precipitates calcium, magnesium and phosphates crystals on the surface of the catheter. This fouling blocks the lumen of the catheter and

Chart 1. Presentation of the papers according to publication year, study design, objectives, key results and conclusions and level of evidence.

Author, journal and year	Study design	Objectives	Key results and conclusions	Level of Evidence
Pigrau C, Rodríguez-Pardo MDR. Enferm Infecc Microbiol Clin, 2008[12].	Systematic review of descriptive studies	To review microorganism mechanisms to form biofilms in IUC.	Results of the analyses of the descriptive studies included in this review: Biofilm formation begins in 3-7 days after insertion and depends on the microorganism and IUC type; Silicone or hydrogel coated catheters are more resistant to bacterial fixation and biofilm formation when compared to the rubber or latex ones; The presence of flagella and urease production by bacteria enhances biofilm formation on the catheter surface.	V
Ramanathan R, Duane TM. Surg Clin North Am, 2014[7].	Systematic review of descriptive studies	To review the pathogenesis, definition, management and prevention of UTI-IUC in the short term.	The biofilm may take 1 to 3 days to form on the IUC surface. Biofilm formation is more likely in latex IUC due to a favorable mix of surface hydrophobic and hydrophilic regions that allows colonization by various microorganisms. The flagella and motility of the most common microorganisms in UTI-IUC (*E. coli* and *P. aeruginosa*) enhance bacterial adhesion to the catheter surface, a feature required for biofilm formation.	V
Stickler DJ. Journal of Internal Medicine, 2014[5].	Systematic review of descriptive studies	To describe biofilm formation by *P. mirabilis* in IUCs.	*P. mirabilis is the main responsible for crystalline biofilm formation in IUCs.*	V
Verma A, Bhani D, Tomar V, Bachhiwal R, Yadav S. Journal of Clinical and Diagnostic Research, 2016[8].	Prospective observational study	To compare bacterial biofilm formation in patients with silicone IUC and silicone coated latex IUC	After 5 days of catheterization, the silicone IUC showed significantly less bacterial colonization than the silicone coated latex catheter (p = 0.03) and biofilm formation was also significantly lower in the silicone catheter in comparison to the silicone coated latex catheter (p = 0.02).	IV
Alves MJ, et al. Journal of Medical Microbiology, 2014[13].	Retrospective observational study	To evaluate biofilm formation ability of bacteria isolated from patients with urinary tract infections; To evaluate the association of distinct variables (age, sex, bacteria) with biofilm formation.	Biofilm forms immediately after catheter insertion Bacterial species (*E. coli*, *K. pneumoniae and P. mirabilis*) (P< 0.001), along with being female (p = 0.022) were the most influencing factors in biofilm formation.	IV
Tenke P, et al. World J Urol, 2012[3].	Systematic review of descriptive studies	To review biofilm formation in UTI-IUC.	Urease producing bacteria like *P. mirabilis* are the main responsible for crystalline biofilm formation in IUC.	V
Niveditha S, Pramodhini S, Umadevi S, Kumar S, Stephen S. Journal of Clinical and Diagnostic Research, 2012[14].	Prospective study, analitical	To evaluate biofilm formation ability of the uropathogens of UTI-IUC.	*E. coli was the main bacterial species to produce in vitro biofilms.*	IV
Hola V, Ruzicka F, Horka Immunol Med Microbiol, 2010[15].	Retrospective Study	To evaluate biofilm formation ability of bacteria isolated from patients with UTI-IUC.	The greatest proportions of biofilm positive strains were found in *E. faecalis* (94.2%), *P. mirabilis* (94%), *Candida tropicalis* (90.8%) and *Staphylococcus aureus* (100%).	VI

enhance urinary reflux and the possibility of progression to acute pyelonephritis, bacteremia, chronic prostatitis, renal infection, sepsis and, in some cases, death[3,13,19].

Other urease-producing bacteria are *P. aeruginosa*, *K. pneumoniae*, *Morganella morganii*, *Providencia* sp and some strains of *S. aureus* and *Staphylococcus* coagulase negative. The production of urease by *P. aeruginosa*, *K. pneumoniae* and, *M. morganii* does not generate alkaline urine and these strains are rarely associated with fouling formation and catheter obstruction[9].

We noticed in this review that the microbiology of biofilm formation process in IUC is a dynamic process that can continuously incorporate new microorganisms with different characteristics. Therefore, a polymicrobial biofilm is common in long-term catheterization and the patient's own urinary tract is the reservoir most of the times[12].

Chart 2. Synthesis of the factors associated with biofilm formation in indwelling urinary catheters according to level of evidence, 2010-2016.

Risk Factors	Description of the factors	Level of Evidence
Related to the microorganism		
Characteristics of the microorganism	Presence of flagella and urease production by bacteria enhances biofilm formation on the catheter surface[3,5,7,11].	V[3,5,7,12]
	P. mirabilis[3,5,13,15]	IV[13]V[3,5]VI[15]
	E. coli[13,14]	IV[13,14]
Microorganism species	*K. pneumoniae*[13]	IV[13]
	E. faecalis[3,13]	IV[13]V[3]
	Staphylococcus sp[3,13]	IV[13]V[3]
	P. aeruginosa[3]	V[3]
Related to the indwelling urinary catheter		
Urinary catheter type	Rubber or latex[7,8,10]	IV[8]V[7,10]
Catheterization time	3-7 days after insertion[10]	V[3,5,7,10]
	Immediately after insertion[3,5,13]	IV[13]
	1-3 days after insertion[7]	
Patient-related factors		
Gender	Female[13]	IV[13]

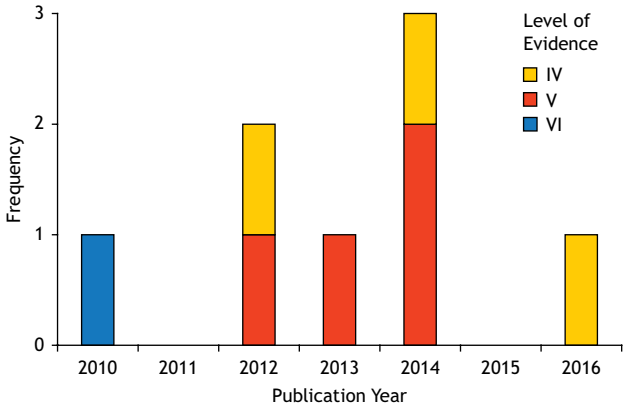

Figure 2. Frequency of the studies included in this review per year and level of evidence, 2010 to 2016.

Factors related to the urinary catheter

Biofilm grows easily in latex IUC because of the favorable composition of its irregular, hydrophobic and hydrophilic surfaces that allow fixation and colonization by various microorganisms[5,7].

Several alternatives to latex catheters have been investigated in order to prevent biofilm formation and, thus, UTI-IUC. Alternatives include silicone catheters or silicone coated catheters impregnated with antimicrobial agents, coated with silver or hydrogel. The use of silicone was considered in order to decrease urethral inflammation and bacterial fixation. A study demonstrated the advantage of catheters made of pure silicone compared to silicone coated latex as to bacterial colonization and biofilm formation[8]. Catheters impregnated with antimicrobial agents and coated with silver were developed to delay bacterial proliferation and the hydrogel surface is theorized with a view to prevent biofilm formation by changing the surface bacterial affinity[7,8,12].

On the other hand, a multicenter study suggested that the use of catheters impregnated with antimicrobial agents reduced the risk of UTI-IUC when compared to the silicone coated latex catheter. However, these results were limited to short-term catheterization and its recommendation is uncertain as to the prevention of biofilm formation and UTI-IUC in periods longer than seven days, in addition to an unfavorable cost-benefit ratio[10,20].

So, the use of catheters impregnated with antimicrobial agents is indicated only when the control of UTI-IUC fails after the global recommendations for prevention were already implemented, such as the restricted use, a aseptic technique of insertion, and an evaluation of the need of maintenance of the catheter[7,10,19]. All types of catheter currently available may be vulnerable to biofilm formation, and, in addition to catheter removal, there is no evidence of effective methods for its prevention or control[5,7,8,10,12,20].

Another critical point is the catheterization time, which is proportional to the risk of biofilm formation. Biofilms develop dynamically, with changes in microbial populations and virulence over time. Biofilms also stimulate microbial growth and its ascent to the urinary system[3,9]. Therefore, the use of the UC must be careful from the evaluation of its indication to insertion, maintenance and removal as soon as possible[10].

Patient related factors

Several patient-related risk factors have been described for the high prevalence of UTI-IUC, like being female, old and having a

severe coexisting disease[3,13,14]. However, only one study, in Portugal, identified being female as an influential factor in biofilm formation in IUC[13]. The fact that urinary tract infections are much more common in women than men is well known due to the short extent of the female urethra and external genitalia anatomy, whose urethral meatus, located in the vaginal vestibule, is more exposed to intestinal microoganisms[10,14].

This study was limited by the lack of randomized primary scientific papers, and showed the predominance of descriptive and review studies. However, the last guideline of the Centers for Disease Control and Prevention for prevention of UTI-IUC dates from 2009 and contains recent knowledge about this problem.

CONCLUSIONS

The main factors associated with biofilm formation in IUC identified in this review were microorganism related, like the presence of flagella, bacterial species (*P. mirabilis*, *E. coli*, *K. pneumoniae*, *Enterococcus faecalis*, *Staphylococcus* sp and *P. aeruginosa)*, urinary catheter type, material (rubber or latex) and being female.

With that, knowing the factors associated with biofilm formation influences the medical staff decisions towards a better analysis as to the type of catheter to be used in health services as well as to the risks to patients (females) and to conditions that enhance adhesion and fixation of microorganisms in IUC. This will contribute consistently to the proposition of effective prevention measures for this event, with a focus on patient safety and care.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.