

Prevention of biofilm formation on artificial pacemakers: is it feasible?

Prevenção da formação de biofilmes em marcapassos artificiais: é viável?

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Abstract

Objective: To identify the antimicrobial agents used in the prevention of biofilm formation on artificial pacemakers.

Methods: Literature review, in order to answer the following question: "What antimicrobial agents are applied to prevent biofilm formation on artificial pacemakers?" The databases PubMed, Web of Science, Scopus, Science Direct, Cochrane, CINAHL, Embase, and LILACS were used in all languages and without time restriction.

Results: The final sample consisted of five primary studies, mostly experimental laboratory ones. The investigations identified agents with promising potential for reduction or inhibition of biofilm formation on pacemakers. An association between physical-chemical agents and pharmacological antimicrobials was highlighted.

Conclusion: Prevention of biofilm formation on pacemakers is feasible. Among the agents that stood out were rifampicin, AIGIS®, aqueous neobactrim formulation, and a plasma coating using a combination of trimethylsilane and oxygen for coating deposition.

Resumo

Objetivo: Identificar os agentes antimicrobianos utilizados na prevenção da formação de biofilme em marcapassos artificiais.

Métodos: Revisão da literatura para responder a seguinte questão: "Quais agentes antimicrobianos são usados para prevenir a formação de biofilmes em marcapassos artificiais?" As bases de dados PubMed, Web of Science, Scopus, Science Direct, Cochrane, CINAHL, Embase e LILACS foram consultadas em todos os idiomas sem restrição de tempo.

Resultados: A amostra final apresentou cinco estudos primários, sendo a maioria experimental. As investigações identificaram agentes com potencial para a redução ou inibição da formação de biofilmes em marcapassos. Destacou-se a associação de agentes físico-químicos e farmacológicos aos agentes antimicrobianos.

Conclusão: A prevenção da formação de biofilmes em marcapassos é viável. Os agentes mais promissores para obter este efeito foram a rifampicina, AIGIS®, a formulação aquosa neobactrim e a cobertura com trimetilsilano e oxigênio em superfícies tratadas com plasma.



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Introduction

Biofilm is defined as community of microorganisms that adhere to solid surfaces and are embedded in a matrix of extracellular polymeric substances (EPS) consisting of carbohydrates, proteins, and nucleic acids, in an environment containing liquids.⁽¹⁾

The EPS matrix is produced by the microorganisms themselves and is organized into complex structures, similar to the honeycombs of a hive,⁽¹⁾ that confer mechanical and antimicrobial resistance. Biofilm acts as a continuous source of contamination and infection, and its properties (the presence of the EPS matrix, the reduced metabolism of microbial cells, transfer resistance genes between the present microbiota, and hindering recognition and attack by host's immune system) represent barriers to its control.^(2,3)

The impact of biofilm on healthcare-associated infections (HAI) has been the subject of investigations over the years. Studies have highlighted its presence on polymeric and hydrophobic surfaces, such as dental and medical implants, mainly in long-term devices.^(2,4-6) Moreover, the vast majority of medical devices can be colonized by biofilm, considering that intravenous catheters, vascular prostheses, prosthetic heart valves, orthopedic devices, and pacemakers are important causes of severe infections.⁽⁷⁾

In the last few decades, increases in the number of therapy applications with cardiovascular implantable electronic devices (CIED) has resulted in increases in implant usage and, consequently, increases in infection rates. In the case of artificial pacemakers, although their implantation be considered a low-complexity procedure with a reduced complication rate, infections are a common occurrence, with incidence ranging from 1% to 5%. These infections commonly occur in the source store (also called the pacemaker store), and their evolution present high morbidity and mortality, since the only effective treatment is mechanical removal of the biofilm and replacement of the old device with a new one.^(8,9)

The aggressiveness of the available treatment reinforces the need for biofilm prevention measures, such as using pacemakers that have been impregnated or coated with antimicrobial substances. The antimicrobial agents act on the initial stage of microbial adhesion to the substrate, before production of the EPS and irreversible biofilm.^(8,10) However, there is no standardization of these practices, which hinders their clinical application and reinforces the need for the current study.

The objective of the current study was to identify the antimicrobial agents that are utilized for the prevention of biofilm formation on artificial pacemakers.

Methods

This is an integrative literature review, an evidence-based practice resource that summarizes past scientific literature and provides a comprehensive understanding of particular phenomena.

Its development included the following steps: establishment of the objective; definition of the inclusion and exclusion criteria for sample selection; definition of the information to be extracted from selected articles in the databases; analysis of the articles; and discussion of the results. The PICO strategy was used to establish the question that guided this research, as follows: P: patients using pacemakers; I: antimicrobial agents; C: was not the object of the research; O: prevention of biofilm formation. Therefore, the following question was asked: What antimicrobial agents are applied in the prevention of biofilm formation on artificial pacemakers?

The following databases were searched for the primary studies: PubMed, Web of Science, Scopus, ScienceDirect, Cochrane, CINAHL, Embase, and Latin American and Caribbean System on Health Sciences Information (LILACS).

The controlled descriptors (MeSH terms, CINAHL titles, and DeCS titles) and keywords used in each database were grouped as follows:

- PubMed and Web of Science: Implantable and Instrumentation or Devices or Equipment and Supplies and Pacemakers and Artificial and

Biofilms or Biofilms and Infections and “Prevention and Control” or Prevention or Control and “Anti-Infective Agents.”

- Cochrane, CINAHL and Embase: Biofilms or Biofilm and “Anti-Infective Agents” or “Agents, Anti-Infective” or “Anti-Infective Agents” or “Anti-Infective Agents” or “Agents, Anti-Infective” or “Microbicides” or “Antimicrobial Agents” or “Agents, Antimicrobial” or “Anti-Microbial Agents” and “Pacemaker, Artificial” or “Artificial Pacemaker” or “Artificial Pacemakers” or “Pacemakers, Artificial” or “Cardiac Pacemaker, Artificial” or “Artificial Cardiac Pacemaker” or “Artificial Cardiac Pacemakers” or “Cardiac Pacemakers, Artificial”.
- LILACS (Portuguese, English and Spanish): “Biofilme” and “Antiinfecciosos” and “Marca-Passo Artificial”.
- Scopus and Science Direct: Biofilms or Biofilm and “Anti-infective Agents” or “Agents, Anti-Infective” or “Anti Infective Agents” or “Anti-infective Agents” or “Agents, Anti-infective” or “Microbicides” or “Antimicrobial Agents” or “Agents, Antimicrobial” or “Anti-Microbial Agents” or “Agents, Anti-Microbial” or “Anti Microbial Agents” and “Pacemaker, Artificial” or “Artificial Pacemaker” or “Artificial Pacemakers” or “Pacemakers, Artificial” or “Cardi-

ac Pacemaker, Artificial” or “Artificial Cardiac Pacemaker” or “Artificial Cardiac Pacemakers” or “Cardiac Pacemakers, Artificial” or “Pacemaker, Artificial Cardiac” or “Pacemakers, Artificial Cardiac”.

The inclusion criteria were: primary studies on the subject, published up to June 2016, in any language. Review surveys, response letters, and editorials were excluded. The searches were carried out in November 2017 by two researchers simultaneously, and were done in three phases:

1. The manuscripts identified in the databases were pre-selected according to the inclusion criteria, and analyzed by reading their titles and abstracts. Removal of duplicate articles left the following: 20 studies in PubMed, 21 in Scopus, 2 in Embase and 6 in ScienceDirect, totaling 49 primary studies. No articles were found in the other searched databases.

2. In the second phase, the articles were analyzed with regard their eligibility, by evaluating the answer to the guiding question, type of research developed, objectives, materials and method, main results, and conclusions, resulting in 16 articles.

3. The third phase consisted of complete reading of all 16 texts, aiming to collect data specific to the review objectives, resulting in the selection of 5 articles (Figure 1).

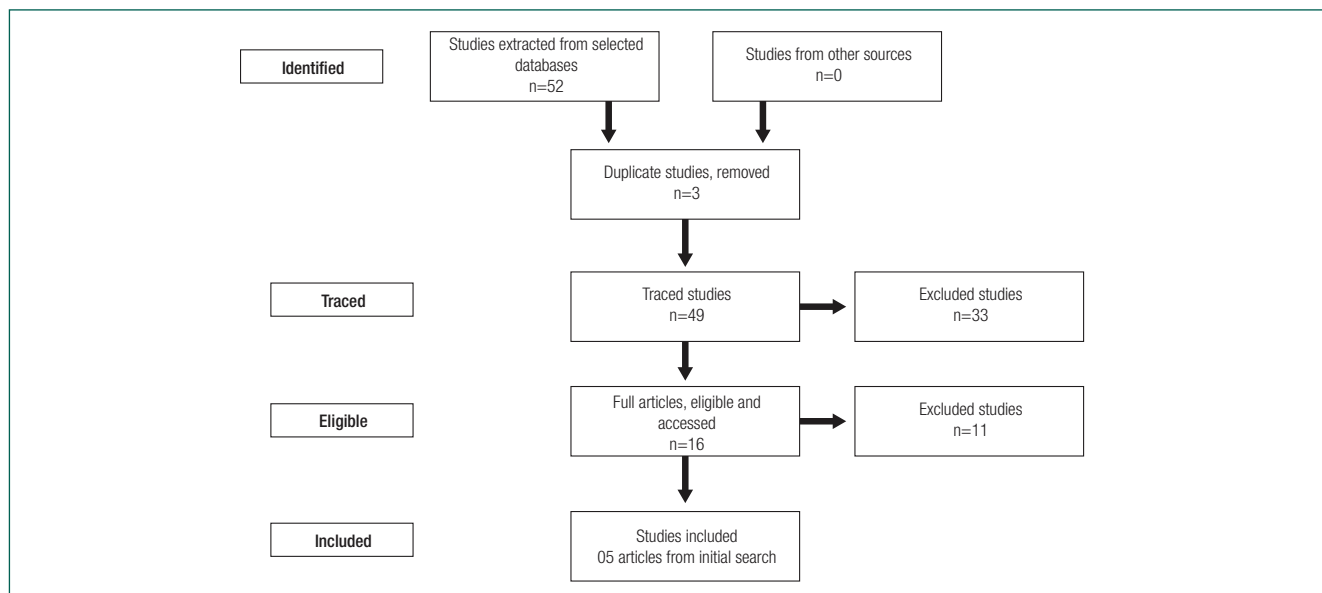


Figure 1. Flowchart for selecting studies retrieved from databases

Chart 1. Distribution of reasons for exclusion of articles

Reasons	Excluded (n= 44)
Involved only bacteria in planktonic form	10
Involved artificial devices other than artificial pacemakers	12
Involved biofilm on artificial pacemakers, but addressed treatment, not prevention	13
Review studies	6
Clinical case studies	2
Protocols	1

The criteria that led to the exclusion of 44 primary studies are presented in chart 1.

Results

The 5 articles included in this review were identified as A1 to A5 for didactic purposes. All the articles were in English and were published from 2010 to 2015. Most were from the PubMed database (75%). In general, the studies aimed to evaluate the potential of antimicrobial, pharmacological, chemical and physical agents in preventing or minimizing biofilm formation on CIED (artificial pacemaker) (Chart 2).

Regarding the type of research, there was a prevalence of experimental in vitro laboratory studies (80%). The investigations identified agents with promising potential to decrease or inhibit biofilm formation.

Combination of physicochemical agents

Xu⁽¹²⁾ presented a new material model consisting of monomeric TMS combined with reactive oxygen for the coating of silicone surfaces, aiming at the prevention of biofilm formation. The scientific literature includes well-founded antimicrobial activities of the TMS model, while oxygen on silicone surfaces has been shown to be efficient in reducing the microbial adherence in the material. Thus, the combination of TMS and reactive oxygen demonstrated a decrease in biofilm formation on the material.

Pharmacological combination of antimicrobials

In order to determine the ability of an antibacterial envelope (AIGIS®) to reduce biofilm formation, one study⁽¹³⁾ utilizing pacemakers in rabbits was de-

veloped. The study used bilateral pockets, one with AIGIS® and the other without it (control). In each pocket, different bacterial loads were inoculated, and after 7 days, the pacemakers were removed and analyzed by scanning and confocal electron microscopy. The results showed that the pacemaker surfaces with antibacterial envelopes had reduced bacterial loads compared to the controls.

Bloom⁽¹⁴⁾ used the same type of antibacterial envelope to determine its potential in the prevention of infections associated with implantable electronic cardiac devices in humans. The research registered a high success rate, since there were only three cases of infection.

Gattringer⁽¹³⁾ investigated the time/effect relationship of rifampicin in *S. epidermidis* biofilms. Incubation of biofilms with rifampicin led to a significant reduction in the calculated optical density ratio of biofilms at 1 minute. At 5, 15, 30 and 60 minutes, no such reductions were observed. The results demonstrated that utilizing rifampicin at a 1.2 mg/mL concentration in physiological solution reduced biofilm formation by *S. epidermidis*, although no bactericidal activity was observed.

Another study⁽⁸⁾ aimed to evaluate the biocompatibility and efficacy of various antimicrobial agents in the prevention of bacterial adhesion to biofilm formation on cardiac devices. The devices were impregnated with seven different solutions of antimicrobial agents (five antibiotics and two antiseptics). They were then contaminated with four bacterial strains (*S. epidermidis*, *S. aureus*, *P. aeruginosa*, and *E. coli*), and incubated for 24 hours. The results showed that, compared to the other antimicrobial agents evaluated, an aqueous formulation of neobactrim presented a better relationship between effectiveness and toxicity, being effective against

Chart 2. Publications included in the review according to title, database, publication year, main research in objective, research type, sample size and main findings

Article ID				
A1	A2	A3	A4	A5
Year				
2010	2015	2010	2014	2011
Database				
PubMed	PubMed	PubMed	Scopus	PubMed
Title				
Time-dependent effects of rifampicin on <i>Staphylococcal biofilms</i> . ¹	Nanoscale plasma coating inhibits formation of <i>Staphylococcus aureus</i> biofilm. ¹²	Efficacy of local rifampin/minocycline delivery (AIGIS®) to eliminate biofilm formation on implanted pacing devices in a rabbit model. ¹³	Prevention of pacemaker infections with perioperative antimicrobial treatment: an <i>in vitro</i> study. ⁸	Implantation success and infection in CIED procedures utilizing an antibacterial envelope. ¹⁴
Aims				
Evaluating the effect/time relationship of rifampicin (1.2 mg/mL) on <i>Staphylococcus epidermidis</i> biofilms in patients with contaminated cardiovascular devices.	To demonstrate the effect of oxygen + plasma coating monomeric trimethylsilane (TMS) on nanometer scale to inhibit the formation of <i>S. aureus</i> biofilms.	Determining the potential of AIGIS® (polypropylene mesh envelope with bioresorbable polymer rifampin and minocycline) in reducing biofilm formation on pacemakers.	Evaluating, <i>in vitro</i> , a pretreatment with antiseptic agents (iodinated povidone and Octenidine + phenoxethanol) and antibiotics (vancomycin, daptomycin, cefuroxime, piperacillin + tazobactam, and neomycin) as prophylaxis for perioperative infection in implanted cardiac devices (artificial pacemakers).	Determining the potential of an antibacterial envelope (polypropylene mesh) for releasing minocycline and rifampin in the generator pocket after pacemaker implantation to prevent infections.
Research type				
Experimental Laboratory.	Experimental Laboratory.	Experimental Laboratory.	Experimental Laboratory.	Retrospective Cohort Study.
Sample size				
30 isolated patients.	Not specified.	Not specified.	96	624 patients
Bacteria belonging to biofilm				
<i>S. epidermidis</i>	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Staphylococcus capitis</i> e <i>Escherichia coli</i>	<i>S. epidermidis</i> , <i>S. aureus</i> , <i>E. coli</i> e <i>Pseudomonas aeruginosa</i>	Not applicable.
Analysis techniques employed				
Electrophoresis pulsed-field gel.	Spectroscopy of x-ray excited photoelectrons.	Scanning Electron Microscopy and Confocal.	Scanning Electron Microscopy and Confocal.	Presence of infectious signs.
Main findings				
1.2 mg/mL rifampicin reduces biofilm formation by <i>S. epidermidis</i> , although it does not present bactericidal activity..	The material showed inhibition of <i>S. aureus</i> biofilms on pacemaker surfaces (stainless steel and titanium). Through this technique, protein absorption related to bacterial adhesion was significantly reduced, and consequently, biofilm formation. The results demonstrate that TMS coated with oxygen is a promising agent in the prevention of biofilm formation on artificial pacemakers..	Evidence from the research suggests that AIGIS® usage may prevent biofilm formation and reduce the microbial burden in cardiac devices.	Showed that a pretreatment of artificial pacemakers consisting of simply immersing them in aqueous solutions of antimicrobial agents significantly reduces bacterial adhesion on their surfaces. Nebacetin was the most effective agent in terms of bacterial growth and cytotoxicity.	CIED implantation procedures using an antibacterial envelope had a high success rate (> 99%) with only three device-related infections.

Gram-positive and negative pathogens, without harming cell vitality. It was shown to be a safe and effective option for impregnation of cardiac devices for the prevention of biofilm formation.

Discussion

The number of procedures for implantation of CIED has increased considerably in the last few decades. Although new technologies make implantation easier, the number of infections related to CIED has doubled in the past two decades, to the

point that some scholars claim that infection rates associated with CIED have increased faster than the number of implantations, resulting in increased morbidity, mortality and expenses to the system.⁽⁸⁾

In addition to the repercussions for infections, the currently available treatment measures are “radical” and make the picture even more dramatic for patients, since complete removal of the entire device, coupled with antibiotic treatment for several weeks, remains the single viable therapy.^(8,15) Additionally, if removal of the infected implant is not feasible, patients must depend exclusively on antibiotic drug therapy.⁽¹⁶⁾

Staphylococci are the most frequently isolated pathogens of infections of implantable electronic cardiac devices, and 50%-75% of infections in CIED are caused by *S. aureus* and coagulase-negative *Staphylococcus*.^(8,11,14) *Staphylococcus* spp. represents one of the most frequent causes of infections in healthcare settings. It is an opportunistic bacterium with a high capacity to spread quickly among people and environments, as well as infecting immunocompromised individuals, greatly increasing morbidity and mortality rates. These microorganisms also have an increased ability to form biofilms.⁽¹⁷⁾

Rifampicin is considered to be the antimicrobial agent of choice for the treatment of CIED, since previous studies have shown that, in combination with other antimicrobials (usually linezolid or teicoplanin), rifampicin is able to prevent vascular infections caused by methicillin-resistant *S. aureus* and *S. epidermidis*.^(11,13,18)

Still using rifampicin, the AIGIS (RX)[®] product was developed to provide a novel approach by creating an antibiotic mesh in which a variety of devices can be implanted to reduce the development of infections in cardiac implants. This product combines rifampicin and minocycline and has been effective in preventing cardiac device colonization and clinical infections by *S. aureus*.⁽¹³⁾ This product is differentiated from others because it has already been tested in patients, with a 99% success rate.⁽¹⁴⁾

Although some studies^(11,12,19) have suggested that the combination of various antimicrobial agents as prophylaxis is effective in preventing infections by common agents, the frequent use of this therapy has increased the rates of resistance of microorganisms to the most-used antimicrobial agents. Although the use of rifampicin has been effective in reducing biofilm formation by *Staphylococcus* spp, it is necessary to rethink non-antibiotic measures to combat or prevent resistance, mainly to rifampicin.

An aqueous formulation of neobactrim can be pointed out as an alternative, since brief impregnation with this antimicrobial agent had a lasting and viable effect and of low cytotoxicity. However, this alternative is still dependent on the use of antibi-

otics, which may contribute to increased resistance over a long period.⁽⁸⁾

New approaches to preventing infections related to devices, which are not dependent on antibiotics, have been tested. Modifying the surface of the biomaterial seems to be a viable alternative, as long as it does not alter the overall properties of the biomaterial,⁽²⁰⁾ as occurred with the TMS/O² coating that was effective in inhibiting *S. epidermidis* biofilm on stainless steel and titanium surfaces (materials used in most CIED, such as artificial pacemakers).⁽¹²⁾ This approach is different because it does not use antibiotics to coat the biomaterials, which contributes to faster degradation of the biomaterial. This technology offers an economical and efficient alternative for preventing the development of *S. aureus* biofilms.

This review is unique in that it addresses biofilm prevention in artificial pacemakers. Although there is a range of review studies addressing the problem of infections in CIED in the literature, none focus on pacemakers, mainly as related to biofilm.

The current study makes an important contribution to public health by synthesizing the main results and recommendations of research on interventions to prevent the formation of biofilms in artificial pacemakers. Compilation of these studies not only allows for the development of new studies exploring the possibilities of new forms of prevention, but also subsidizes institutional protocols capable of preventing the formation of biofilms. The results of the current study can be extrapolated to other materials common in other prostheses and orthoses, expanding its application in clinical practice.

This study has some limitations. The main one is its methodology: Because it is an integrative review, the results reflect a portrait of the reality investigated by the primary studies. Even if the aim were to compare interventions, the limited number of randomized clinical trials published in the databases searched would make such a finding impossible.⁽²¹⁾ Another limitation is the fact that not all the studies surveyed affirmed whether there was a sample calculation or randomization to delimit the sample.

Conclusion

An analysis of the scientific literature indicates that there is a concentration of studies aiming at the prevention of biofilm formation in implantable artificial pacemakers by inhibiting the initial stages of bacterial adhesion. In addition, some antimicrobial agents (pharmacological, chemical and physical) were evaluated for efficacy in the prevention of biofilm formation in artificial pacemakers, with emphasis on rifampicin, AIGIS® (combination of rifampicin with minocycline), an aqueous neobactrim formulation, and covering the surface of the device with a combination of monomeric trimethylsilane and reactive oxygen.

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