

**PRESENCE OF BIOFILM AND CONSEQUENCES FOR WOUND HEALING: NARRATIVE REVIEW****PRESENCIA DE BIOPELÍCULA Y CONSECUENCIAS PARA LA CICATRIZACIÓN DE HERIDAS: REVISIÓN NARRATIVA****PRESENÇA DO BIOFILME E AS CONSEQUÊNCIAS PARA CICATRIZAÇÃO DA FERIDA: REVISÃO NARRATIVA**

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**Submission:** 12-06-2024

**Approval:** 21-05-2025

**ABSTRACT**

**Introduction:** Biofilms are microscopic structures, surrounded by an encapsulation of microorganisms of different species that directly interfere with the individual's immune response. **Objective:** Review clinical aspects of the presence of biofilm for the wound healing process. **Methods:** Narrative literature review. The descriptors used in the literature search were selected from controlled vocabularies, descriptors DeCS/MeSH: Biofilms, Healing, Wounds and Injuries, Biofilms, Wound Healing, Wounds and Injuries. And to obtain a broad search of the topic researched by the MEDLINE and LILACS databases, the descriptors were used alone or in combination, along with the Boolean operators AND and OR. The search and analysis period for the selected articles took place between the months of March and July 2023. **Results:** Biofilms are microscopic structures of microorganisms that prevent bacterial recognition and elimination, worsening infection and prolonging inflammation. Chronic wounds, such as venous and diabetic foot ulcers, are especially affected, presenting high inflammatory activity and difficulty healing. Clinical detection of biofilms is challenging and their presence may be indicated by signs such as persistent local infection, excessive moisture, and friable granulation tissue. Treatment requires a multidisciplinary approach and the use of innovative technologies such as silver-impregnated dressings and other antimicrobial treatments. **Conclusions:** The research seeks to contribute to the diagnosis and adequate treatment of biofilm, improving wound care and facing the challenges posed by biofilm, it is expected to improve wound healing and the quality of life of affected patients.

**Keywords:** Biofilms; Wound Healing; Injuries.

**RESUMEN**

**Introducción:** Los biofilms son estructuras microscópicas, rodeadas por una encapsulación de microorganismos de diferentes especies que interfieren directamente con la respuesta inmune del individuo. **Objetivo:** Revisar aspectos clínicos de la presencia de biofilm para el proceso de cicatrización de heridas. **Métodos:** Revisión de la literatura narrativa. Los descriptores utilizados en la búsqueda de literatura se seleccionaron de vocabularios controlados, descriptores DeCS/MeSH: Biofilms, Healing, Wounds and Injuries, Biofilms, Wound Healing, Wounds and Injuries. Y para obtener una búsqueda amplia del tema investigado en las bases de datos de la MEDLINE y LILACS, se utilizaron los descriptores solos o en combinación, junto con el booleano operadores Y y O. El período de búsqueda y análisis de los artículos seleccionados se desarrolló entre los meses de marzo y julio de 2023. **Resultados:** Las biopelículas son estructuras microscópicas de microorganismos que impiden el reconocimiento y eliminación bacteriana, empeorando la infección y prolongando la inflamación. Las heridas crónicas, como las úlceras venosas y del pie diabético, se ven especialmente afectadas, presentando alta actividad inflamatoria y dificultad de cicatrización. La detección clínica de biopelículas es un desafío y su presencia puede estar indicada por signos como infección local persistente, humedad excesiva y tejido de granulación friable. El tratamiento requiere un enfoque multidisciplinario y el uso de tecnologías innovadoras como apósitos impregnados de plata y otros tratamientos antimicrobianos. **Conclusiones:** La investigación busca contribuir al diagnóstico y tratamiento adecuado del biofilm, mejorando el cuidado de las heridas y enfrentando los desafíos que plantea el biofilm, se espera mejorar la cicatrización de las heridas y la calidad de vida de los pacientes afectados.

**Palabras clave:** Biofilms; Cicatrización de Heridas; Lesiones.

**RESUMO**

**Introdução:** Biofilmes são estruturas microscópicas, envoltas de um encapsulado de microorganismos de diferentes espécies que interferem diretamente na resposta imunológica do indivíduo. **Objetivo:** Revisar aspectos clínicos da presença do biofilme para o processo de cicatrização de feridas. **Métodos:** Revisão narrativa da literatura. Os descritores utilizados na busca da literatura foram selecionados a partir de vocabulários controlados, descritores DeCS/MeSH: Biofilms, Healing, Wounds and Injuries, Biofilms, Wound Healing, Wounds and Injuries. E para obter uma busca ampla do tema pesquisado pelas bases de MEDLINE e LILACS, os descritores foram utilizados isoladamente ou em combinação, juntamente com os operadores booleanos AND e OR. O período de busca e análise dos artigos selecionados ocorreu entre os meses de março e julho de 2023. **Resultados:** Biofilmes são estruturas microscópicas que impedem o reconhecimento e a eliminação bacteriana, agravando a infecção e prolongando a inflamação. As feridas crônicas, como úlceras venosas e do pé diabético, são especialmente acometidas, apresentando atividade inflamatória e dificuldade de cicatrização. A detecção clínica de biofilmes é desafiadora e sua presença pode ser indicada por sinais como infecção local persistente, umidade excessiva e tecido de granulação friável. O tratamento requer uma abordagem multidisciplinar e o uso de tecnologias inovadoras, como curativos impregnados de prata e outros tratamentos antimicrobianos. **Conclusões:** A pesquisa busca contribuir para o diagnóstico e tratamento adequado do biofilme, melhorando o cuidado com as feridas e frente aos desafios impostos pelo biofilme, espera-se melhorara cicatrização das feridas e a qualidade de vida dos pacientes acometidos.

**Palavras-chave:** Biofilmes; Cicatrização; Lesão.



## INTRODUCTION

Wounds are caused by local and/or systemic factors that impair the tissue repair process and contribute to the stagnation of lesions, often resulting from the presence of biofilm. They can be classified as acute and/or chronic, and often challenge healthcare professionals due to the significant tissue involvement, the presence of infection, and the consequent formation of biofilm <sup>(1)</sup>.

Biofilms are microscopic structures, surrounded by an encapsulation of microorganisms of different species that directly interfere with the individual's immune response. When they are present in the lesion, they prevent the recognition and elimination of microorganisms, which can contribute to the increased risk of tolerance and resistance to the proposed treatment. They are directly associated with the difficulty in the healing process that results from local chronic inflammation, but they can also be found in acute wounds, including surgical wounds <sup>(2)</sup>.

Bacterial biofilms are commonly found in chronic wounds, which contributes to their persistence. Venous ulcers can remain open for years, as the host's immune response is often unable to eliminate the biofilm, making healing difficult. Therefore, inadequate blood supply to the infected area can result in a decreased immune response, increasing virulence and tissue necrosis, which can occur in diabetic foot ulcers. In addition, it has been shown that biofilms reach nutrients in the plasma and exudate present in the wound bed <sup>(3)</sup>.

New technologies are being introduced to wound treatment, which stand out mainly for providing great benefits that were previously difficult to achieve through conventional treatments, for wounds and critical injuries. These technologies seek to promote faster healing, in addition to regression of pain caused by the severity of the injury. All these factors, when combined, will provide the patient with greater comfort, already during treatment, and an improvement in their quality of life <sup>(4)</sup>.

Treating wounds is a complex process in itself, given the countless factors that contribute to their development and can also delay healing, such as economic, social, biological, and other factors. To achieve this, a qualified multidisciplinary team is essential to provide care with an emphasis on the problem, working directly on the treatment and prevention of wounds, which can result as secondary pathologies to an underlying disease process in a rapid and intense manner <sup>(5)</sup>.

Therefore, this research is justified because it addresses a current clinical issue, with important implications for clinical practice and patient well-being, aiming to effectively contribute to the diagnosis and treatment of biofilm, effectively improving care for people with wounds.

Thus, this work aims to describe the presence of biofilm and the consequences for wound healing, listing the main forms of treatment, carrying out a bibliographic survey in the main databases, identifying clinical signs of biofilm present in the wound, verifying the

factors that contribute to the emergence of biofilm and describing the treatment for removing biofilm.

## **METHODS**

### **Type of study**

This is a study conducted through a narrative review. The research stages consisted of developing the guiding question of the study, selective search for articles, extraction of the data obtained, analysis of the content of the articles and synthesis of the results <sup>(6)</sup>.

### **Identifying the guiding question**

This study was developed to answer the

### **Establishment of inclusion and exclusion criteria**

The inclusion criteria were articles in Portuguese and English that addressed topics such as chronic wounds, biofilm in wounds, and the consequences of biofilm on the wound healing process. The exclusion criteria were articles that were duplicated in the databases and that were not written in the chosen language (English or Portuguese).

### **Data sources and search strategy**

The search for articles took place in the National Library of Medicine National Institutes of Health (MEDLINE) and Latin American and Caribbean Literature in Health Sciences (LILACS) databases.

### **Search and selection procedures**

The descriptors used in the literature

guiding question: what are the consequences of the presence of biofilm in the wound healing process? The elaboration of the guiding question occurred through the PICO strategy. Where "P" refers to the research problem (Biofilm in wounds), "I" refers to the phenomena of interest (The consequences for wound healing), "Co" refers to the context (presence of biofilm in wounds).

search were selected from controlled vocabularies, descriptors in Health Sciences/Medical Subject Headings (DeCS/MeSH): Biofilms, Healing, Wounds and Injuries, Biofilms, Wound Healing, Wounds And Injuries. And to obtain a broad search of the researched topic in the databases, together with the Boolean operators AND and OR, to refine searches and obtain more precise and relevant results, adapted for each database, ensuring the scope of the research.

The search and analysis period of the selected articles took place between March and July 2023. The instrument was chosen due to its simplicity and to meet the guiding question of the study: what are the consequences of the presence of biofilm in the wound healing process?

After the search for articles in the databases mentioned above, the search was

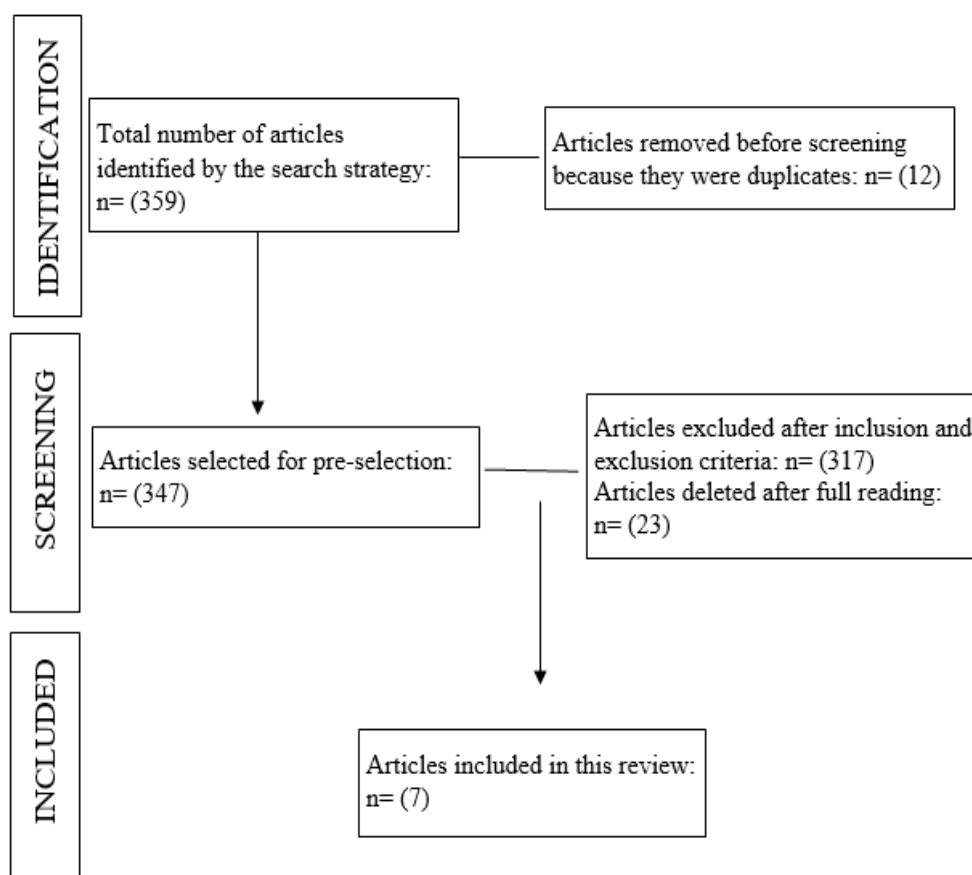


limited to 359 articles, of which 119 were related to MEDLINE and 240 to LILACS. As they did not meet the inclusion criteria and the proposed theme, 345 articles were excluded; therefore, 14 articles were included, which met the eligibility

criteria.

Flowchart 1 below demonstrates the search strategy and selection of articles that will be included in this narrative review.

**Figure 1** - Flowchart of identification, screening and inclusion of articles.



**Source:** Own authorship (2024).

### **Procedures for extracting, organizing and summarizing data**

Data were extracted from the included studies through careful selection of information sources, such as relevant scientific databases and journals, and specific search terms related to the topic mentioned above.

The articles were then analyzed,

excluding those that did not meet the predetermined criteria. Relevant data were then extracted and organized according to the main thematic categories, such as the mechanisms of biofilm formation and impact on wound healing, diagnostic and treatment strategies, and challenges and gaps in research.

In the analysis and summarization of the

data, the studies were grouped according to the main themes and results found, identifying patterns, trends and gaps in knowledge, and performing a synthesis of the main findings, highlighting the mechanisms by which biofilm affects wound healing and the possible therapeutic strategies discussed in the literature.

### **Assessment of included studies**

The evaluation of the included studies was conducted meticulously, considering the relevance to the topic addressed, thus ensuring the relevance of the results to achieve the objectives of this narrative review.

### **Analysis/Interpretation of results**

The analysis and interpretation of the results were carried out based on the synthesis of the studies included in the narrative review, in which the main trends, patterns and gaps in knowledge about the presence of biofilm and its consequences on wound healing were identified and discussed, highlighting the relevance of the findings for clinical decision-making and the development of targeted interventions.

### **Presentation of the review**

Data synthesis was performed qualitatively, highlighting the main findings and trends identified in the included studies. Narrative approaches were used to organize and present the information in a clear and understandable way. A quantitative meta-analysis was not performed due to the heterogeneity of the included studies.

## **RESULTS/DISCUSSION**

### **BIOFILM PHYSIOLOGY**

Biofilm is characterized by a thick layer of microorganisms that group together to form microbial communities. It binds to surfaces with a layer of polysaccharides called extracellular polymeric substance (EPS). The EPS is formed by polysaccharides, extracellular DNA, proteins, lipids, surfactants, flagella, and pili. This polymeric matrix preserves microorganisms, since it originates around and on top of microbial growth, favoring the evolution of this community and protecting it from threats to its survival. Biofilm is porous and allows efficient access of nutrients and elimination of waste <sup>(7, 8, 9)</sup>.

In general, microbial growth produces two types of cells: independent living cells and sessile cells, which, when aggregated, form biofilms, which can be composed of Gram-positive bacteria, Gram-negative bacteria, or a combination of both, protozoa, algae, and even viruses. In most biofilms, however, microorganisms represent less than 10% of the dry matter, with the remaining 90% being made up of the polymer matrix <sup>(7)</sup>.

It is worth noting that the cells that make up a biofilm are involved in a complex network of interactions where the main objective is to maintain the survival and organization of the community. This system is called Quorum sensing (QS) <sup>(9)</sup>.

In the aforementioned system, bacteria control the entire behavior of the bacterial community, synthesizing and secreting signaling molecules, also known as autoinducers (AIs). Bacteria use this system to communicate and coordinate the structure and function of bacterial biofilms<sup>(10)</sup>.

To do so, it is necessary for the bacteria that generate these molecules to signal to other nearby bacteria. When the bacteria detect that a threshold concentration of AIs has been reached, they can modify the expression and behavior of their genes. Furthermore, microorganisms share genetic material, thus increasing the survival of this structure. In addition to altering bacterial behavior, QS-associated AIs can also be incorporated into the crosstalk between the host and the microorganism<sup>(10)</sup>.

## CONSEQUENCES OF BIOFILM ON WOUND HEALING

Biofilms can cause significant delays in healing, and professionals need to consider their antimicrobial resistance to achieve healing. It is known that the presence of biofilm within the wound and the abundance of microorganisms interfere with the inflammatory phase and increase the recruitment of neutrophils and macrophages to the wound bed. Therefore, during this process, bacterial species encourage other molecular mechanisms to create an environment with high inflammatory activity to the detriment of subsequent phases, facilitating the delay of the healing process and the

maintenance of the long duration of the wound<sup>(11)</sup>.

Biofilm activates chronic and prolonged inflammatory responses, modifying the course of skin healing. As in any inflammatory state, there is infiltration of monocytes (macrophages, lymphocytes and plasma cells), with tissue destruction, vascular hyperproliferation, permanent replacement of connective tissue and fibrosis<sup>(12)</sup>.

## IDENTIFICATION OF BIOFILM IN THE WOUND

The diagnosis of biofilm infections is based primarily on clinical findings because, by their very nature, they are difficult to detect. Several methods have been proposed to detect biofilms in laboratory settings, but these advances have not been as great in clinical settings<sup>(13,14)</sup>.

Biofilm infections are often related to chronic infections and remain at the site of infection, usually in the case of implanted devices. In addition, biofilms are capable of producing silent or subclinical infections that cause a diminished inflammatory response from the host and, therefore, are more difficult to detect and treat<sup>(13)</sup>.

On abiotic surfaces, biofilms are easily visible to the naked eye when they have a certain size and color. However, the macroscopic identification of biofilms on biological surfaces, i.e., chronic wounds, is speculative and based on the color caused by sessile aggregates or dominant planktonic microorganisms<sup>(15)</sup>.



When biofilms cannot be distinguished visually, other indirect clinical indicators may indicate their presence, such as:

Clinical signs of local infection (redness, pain, odor, etc.); Excessive moisture; Friable granulation tissue; Persistent infection; Failure of antimicrobial treatment and recurrence of infection; Negative culture results despite signs of bacterial colonization or high suspicion of clinical infection; Wound remains recalcitrant<sup>(16)</sup> (p.29).

However, despite advances in laboratory techniques for biofilm detection, microbiological techniques may still be less sensitive than, for example, culture. This is because, even when cells can be detected, there are limiting factors, such as slow-growing variants. Culture techniques may not be effective due to biofilm heterogeneity, the presence of mixed species, and the involvement of fastidious bacterial strains, among other factors<sup>(13)</sup>.

There are no standardized techniques for biofilm detection in the clinical setting, although there is a great need and shortage. However, molecular techniques hold promise due to recent advances in biofilm detection and the use of biofilm-associated biomarkers and imaging techniques. Another promising approach is the use of biomarkers, since, when bound to biofilms, they can detect unique molecules or stimulate specific hosts to respond to them. Antibodies may not be detectable during acute infection, but can be used to detect biofilm-related infections<sup>(9)</sup>.

Thus, proteins are the main substances used as biomarkers for biofilm-producing

bacteria. Biofilm images provide spatial information that can help analyze other conventional methods, improving them<sup>(7)</sup>.

Therefore, among the unconventional methods for detecting biofilms, studies based on bioimpedance can be mentioned, in which electric currents and surface acoustic waves are used through vibrations<sup>(7)</sup>.

## EVALUATION AND TREATMENT OF BIOFILM INJURY

The dressing technique is the first nursing procedure that should be performed when evaluating a wound. It is through this approach that the nurse, after careful evaluation, can autonomously implement the care necessary for healing of the established wounds, also aiming at the identification of biofilm<sup>(17)</sup>.

New approaches to the treatment of chronic wounds are receiving increasing attention, such as Biofilm-Focused Wound Care (BFWC), which involves the evaluation of wound properties and the use of debridement methods to remove necrosis and slough<sup>(18)</sup>.

Wounds that do not heal even after the application of strict treatment standards should be brought to the attention of a health professional, with the aim of performing an examination to carefully inspect for direct or indirect signs of biofilm. Although moisture is essential for wound healing, low humidity or the presence of high levels of exudate can make the environment prone to biofilm formation. Therefore, moisture control is essential to optimize the wound bed to promote healing and

minimize the possibility of microbial growth<sup>(19)</sup>.

Currently, biofilm control can be developed in several ways, through the use of substances that interfere with adhesion and QS, phage therapy, debridement, and ultrasound with low-frequency acoustic energy. In addition, it is also possible to find subatmospheric pressure therapy, hyperbaric oxygen, alternative tissue bioengineering, and topical therapies as treatments<sup>(20)</sup>.

Topical antiseptics, such as iodine-based medications, chlorhexidine, polyhexamethylene biguanide (PHMB), and silver-based products are used to prevent and treat wounds. Systematic reviews have shown that topical application of PHMB or silver-impregnated dressings creates an environment conducive to the healing process, controls pain, and reduces microbial load. However, small sample sizes, methodological flaws, inconsistent measurements, and short-term patient follow-up make it difficult to provide evidence for clinical practice<sup>(20)</sup>.

Any selected product needs to be used continuously for at least 7 to 10 days and reassessed before stopping or continuing treatment. A recent consensus recommends the use of antimicrobials, especially silver-based dressings, for up to 2 weeks. After 2 weeks, it is essential to evaluate the efficacy of the treatment by improving tissue repair and looking for signs of infection<sup>(21)</sup>.

## FINAL CONSIDERATIONS

Through research and reading, we can see that wounds resulting from local or systemic factors directly impair the tissue repair process, since the biofilms present in these lesions interfere with wound healing.

The biofilms present in wounds, which are visualized microscopically, have important characteristics that we can identify in lesions without the aid of a microscope, through clinical signs and wound characteristics, the high inflammatory activity that they can generate, and with this an increase in the microbial load, an increase in exudate, uncontrolled moisture, type of tissue and edges.

Therefore, establishing the appropriate and necessary treatment for removing biofilms requires a thorough and careful assessment in order to choose the ideal conduct for wound management and consequently promote an ideal healing process, using antiseptic solutions that promote effective cleaning and help remove these microorganisms so that the dressing and/or related material chosen to be applied to the wound bed helps in healing.

It is extremely important that during the assessment of the wound and the choice of treatment by the nursing professional, it is identified whether or not there is the presence of biofilm, with the aim of removing all microbial load present and thus implementing specific care with cleaning and the choice of coverage to be placed on the lesion and thus providing the patient with effective assistance based on kinetic knowledge.



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#### **Declaration of Conflict of Interest**

Nothing to declare.

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