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Review Article

Evidence for biofilm treatment in chronic wounds: narrative review

Evidências no tratamento de biofilme em feridas crônicas: revisão narrativa

Evidencias en el tratamiento de biofilm en heridas crónicas: revisión narrativa

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ABSTRACT

Background and Objectives: Microbial load predicts failures in chronic wound treatment. The objective was to investigate the available evidence on biofilm treatment in chronic wounds in adults. **Content:** Narrative review using descriptors such as "Treatment" and "Biofilm" in searches across major databases from February to July 2024, including articles from the last 10 years, excluding preclinical studies, and ensuring quality with the SANRA checklist. The initial search identified 1,323 articles, of which 780 were excluded. After screening, 21 articles were read in full, resulting in the inclusion of 11 in the review. **Conclusion:** The study demonstrates the effectiveness of therapeutic approaches for treating biofilms in chronic wounds. Surfactant-based dressings with silver sulfadiazine proved effective, especially when applied early. The AQUACEL™ Ag+ dressing showed promising results in chronic venous ulcers, and olive oil extract of *C. oestroides* emerged as an alternative for refractory patients. Microbial load was identified as a predictor of treatment failures, while fluorescence imaging and antibiofilmogram technology improved antimicrobial management. Surfactant-based gel shows contradictory results in bacterial community and cadexomer iodine reduces microbial load although without statistical significance in healing. Limitations such as sample sizes and lack of methodological rigor indicate the need for further research.

Keywords: *Wounds and Injuries. Gram-Positive Bacteria. Gram-Negative Bacteria. Bacterial Adhesion. Wound Healing.*

RESUMO

Justificativa e Objetivos: A carga microbiana prediz falhas no tratamento de feridas crônicas. O objetivo foi investigar as evidências disponíveis sobre o tratamento de biofilmes em feridas crônicas em adultos. **Conteúdo:** Revisão narrativa com uso de descritores como "Treatment" e "Biofilm" em buscas realizadas entre fevereiro e julho de 2024 nas principais bases de dados, incluindo artigos dos últimos 10 anos e excluindo estudos pré-clínicos. O checklist SANRA foi adotado para garantir a qualidade. Na busca inicial foram identificados 1.323 artigos, dos quais 780 foram excluídos. Após a triagem, 21 artigos foram lidos na íntegra, resultando na inclusão de 11 na revisão. **Conclusão:** O estudo mostra a eficácia de abordagens terapêuticas para o tratamento de biofilmes em feridas crônicas. Os curativos surfactantes com sulfadiazina de prata mostraram-se eficazes, especialmente quando aplicados precocemente. O curativo AQUACEL™ Ag+ teve resultados promissores em úlceras venosas crônicas, e o extrato de azeite de oliva de *C. oestroides* surgiu como uma alternativa para pacientes refratários. A carga microbiana foi identificada como preditora de falhas no tratamento, enquanto a imagem de fluorescência e a tecnologia de antibiofilmograma melhoraram a gestão antimicrobiana. Contudo, o gel surfactante mostra resultados contraditórios na comunidade bacteriana e o iodo cadexômero reduz a carga microbiana, mas sem significância estatística em cicatrização. Limitações como tamanhos de amostra e a falta de rigor metodológico sinalizam a necessidade de pesquisas adicionais.

Descritores: *Ferimentos e lesões. Bactérias Gram-Positivas. Bactérias Gram-Negativas. Camada Biológica. Cicatrização.*

RESUMEN

Justificación y Objetivos: La carga microbiana predice el fracaso del tratamiento de heridas crónicas. El objetivo fue investigar la evidencia disponible sobre el tratamiento de biofilm en heridas crónicas en adultos. **Contenido:** Revisión narrativa que utilizó descriptores como "Treatment" y "Biofilm" en búsquedas en las principales bases de datos entre febrero y julio de 2024, incluyendo artículos de los últimos 10 años, excluyendo estudios preclínicos, y garantizando calidad con el checklist SANRA. La búsqueda inicial identificó 1.323 artículos, de los cuales 780 fueron excluidos. Después del cribado, 21 artículos fueron leídos en su totalidad, resultando en la inclusión de 11 en la revisión. **Conclusión:** El estudio demuestra la eficacia de abordajes terapéuticos para el tratamiento de biofilm en heridas crónicas. Los apósitos surfactantes con sulfadiazina de plata se mostraron eficaces, especialmente cuando se aplican de forma precoz. El apósito AQUACEL™ Ag+ mostró resultados prometedores en úlceras venosas crónicas, mientras que el extracto de aceite de oliva de *C. oestroides* surgió como una alternativa para pacientes refractarios. La carga microbiana fue identificada como un factor predictor del fracaso terapéutico; por su parte, la imagen de fluorescencia y la tecnología de antibiofilmograma mejoraron la gestión antimicrobiana. No obstante, el gel surfactante presenta resultados contradictorios en cuanto a su efecto sobre la comunidad bacteriana, y el cadexómero yodado, aunque reduce la carga microbiana, no alcanzó significancia estadística en la cicatrización. Limitaciones como el tamaño de las muestras y la falta de rigor metodológico señalan la necesidad de investigaciones adicionales.

Palabras Clave: *Heridas y lesiones. Bacterias Grampositivas. Bacterias Gramnegativas. Adhesión Bacteriana. Cicatrización de Heridas.*

INTRODUCTION

Chronic wound healing is a complex multifactorial process, essential for restoring tissue integrity and maintaining the skin barrier. Chronic wounds, characterized by prolonged healing, arise as a result of trauma, pathological conditions, or systemic factors.[1] The healing process can last more than six weeks and face complications, such as biofilms and infections, which delay recovery.[2–5]

Pressure injuries, diabetic ulcers, and chronic vasculogenic wounds are common conditions, especially in the older adult population, whose proportion is rising globally. The prevalence of these conditions is significantly elevated in individuals with risk factors such as venous insufficiency, poor arterial perfusion, diabetes, and hypertension.[6,7]

Recent studies have highlighted the magnitude of the costs associated with wound treatment. In Brazil, a comparative study in Primary Health Care indicated that the daily change of conventional dressings generated an estimated cost of R$ 101,030.58, considering 15 patients and 9,303 days of treatment. This figure does not include other products and medications, suggesting that the total cost may be substantially higher.[8]

The presence of biofilms in chronic wounds is a significant complication that delays healing. Biofilms are complex microbial communities, composed of bacteria, fungi, and algae, that adhere to surfaces and produce a protective extracellular matrix.[9,10] This formation hinders the host's immune response and confers resistance to antimicrobials.[11,12] Studies indicate that approximately 60% of patients with infected chronic wounds present with biofilms.[13,14]

Lack of proper management can result in infections and sepsis, leading to serious complications such as amputations and mortality.[7,15] In addition to physical impacts, wounds cause pain, body image disturbances, and functional limitations, affecting self-care and quality of life for patients, who may face stigmatization and depression.[2,16]

High microbial load is a predictive factor for treatment failure.[17] Debridement, followed by antimicrobial therapy, is recommended for biofilm management, aiming to optimize healing.[13] Studies investigate various active ingredients, including silver sulfadiazine, cadexomer iodine and polymyxin B; furthermore, the availability of AQUACEL™ Ag+ dressing and biofilm-disrupting gels makes the therapeutic choice complex.[7,13,18–20] Thus, the aim of this study is to investigate the available evidence on the treatment of biofilms in chronic wounds in adults.

METHODS

This is a narrative literature review on the treatment of biofilm in chronic wounds in adults. The PICO strategy was used, (P = population): adults with chronic wounds; (I = intervention): treatments; (C = comparison): standard treatment; (O = outcome): biofilm, microbial communities. The search strategy was performed using the following descriptors: "Humans", "Chronic Wound", "Pressure Ulcer", "Diabetic Foot", "Venous Ulcer", "Varicose Ulcer", "Treatment" and "Biofilm". The searches were conducted between February 2024 and July 2024 in the following databases: PubMed, Scopus, Web of Science, LILACS, Virtual Health Library (BVS), Embase, SciELO, Cochrane Wounds Group Specialized Register, Brazilian Registry of Clinical Trials (REBEC), The Cochrane Central Register of Controlled Trials, The EU Clinical Trials Register, and the WHO International Clinical Trials Registry.

Eligibility criteria included articles published between 2013 and 2023, referring to studies with humans (≥ 18 years) with chronic wounds of any etiology (pressure injuries, diabetic, venous or arterial ulcers). Studies that evaluated new treatments, combinations of treatments, or experimental treatments compared to standard treatments were considered, as well as any type of treatment tested as chemical agent (antibiotics, iodine, silver, nanoparticles, papain, herbal or other medicinal active ingredients – in creams, ointments, sprays, gels, oils, etc.) or devices. Exclusion criteria: preclinical studies (in vitro and with animals), letters to the editor, books, book chapters, review studies, conference papers, retracted articles, theses, dissertations, and guidelines.

The studies were organized using the Rayyan program, which assists in literature review. Researchers selected and evaluated articles based on predefined criteria and systematically extracted data using Rayyan tools.[21] The Scale for the Assessment of Narrative Review Articles (SANRA) checklist was followed to ensure the quality of this paper. Since this is a literature review, approval from an ethics committee was not required.

RESULTS AND DISCUSSION

In the initial search, 1,323 articles were identified. Of these, 780 were excluded for not meeting the inclusion criteria, and 523 were duplicates. After this screening, 21 articles were selected for full-text reading, 11 of which met the eligibility criteria and were included in the review (Table 1).

Table 1. Summary of selected studies, Porto Alegre, Rio Grande do Sul, 2025.

Summary of selected studies					
Study title	Author/Year/ Country	Type of study	Objective	Sample	Main results
Efficacy of a new multifunctional surfactant-based biomaterial dressing with 1% silver sulfadiazine in chronic wounds	Zolb et al., 2014 Austria	Multicenter, prospective, and observational study	To describe the effects of treating patients with chronic wounds using a surfactant-based gel dressing with 1% silver sulfadiazine.	The study included 226 patients with chronic wounds, with a minimum duration of eight weeks and a size greater than 1 cm². The wounds were classified as follows: 72 arterial ulcers (32%), 73 venous ulcers (32%), 23 mixed ulcers (10%), 41 diabetic/neuropathic wounds (18%), and 17 other wounds (8%), including post-traumatic, post-operative, and burn wounds. A total of 88 patients received standard treatment in the unit, while 138 patients initiated treatment with a surfactant-based 1% silver sulfadiazine gel.	In the standard group, 73% of patients healed or showed improvement, with 60% healing in a median of 17 weeks. In the group using a surfactant-based 1% silver sulfadiazine dressing, 86% healed or improved, with 73% healing in a median of 12 weeks. Reports indicated better adherence, reduced pain, and a favorable side effect profile. Economic analyses showed significantly reduced treatment costs compared to the standard.
Local wound management factors related to biofilm reduction in the pressure ulcer: a prospective observational study	Koyanagi et al., 2021 Japan	Multicenter, prospective, and observational study	To explore effective local management methods for reducing biofilm areas in critically colonized pressure injuries.	The sample consisted of 34 patients with pressure injuries deeper than the dermis and in a state of critical colonization. The primary outcome was the change in the ratio of biofilm area to pressure injury area over one week, investigating its relationship with local wound treatment. Six types of topical treatment were used: 1. Iodine ointment; 2. Prostaglandin E1 ointment; 3. Silver sulfadiazine ointment; 4. Hydrocolloid dressing; 5. Foam/silicone dressing; 6. Gauze dressing. The blotting method was used to determine the biofilm area, calculating the change by subtracting the baseline proportion from the proportion after one week.	The study results showed that the proportion of biofilm area after one week was significantly lower with the use of iodine ointment, with a reduction of 0.26 units (p=0.02) compared to the groups that did not use iodine ointment. Multivariate analysis confirmed that the use of iodine ointment was strongly associated with biofilm reduction. It is concluded that iodine ointment is effective in treating critically colonized pressure injuries, contributing to improved healing.
Effect on total microbial load and community composition with two versus six-week tropical Cadexomer Iodine for treating chronic biofilm infections in diabetic foot ulcers	Malone et al., 2019 Australia	Prospective cohort pilot study	To compare two versus six weeks of topical antimicrobial therapy with cadexomer iodine in patients with diabetic foot ulcers (DFU) complicated by chronic biofilm infections.	18 patients with DFU were recruited over 18 months at a tertiary hospital. DFU with suspected chronic biofilm infection were included. Patients were randomized to receive two or six weeks of topical cadexomer iodine treatment. Ulcer biopsies were collected before and after treatment, subjected to deoxyribonucleic acid (DNA) sequencing and quantitative polymerase chain reaction (PCR) to assess microbial load, community composition, and bacterial diversity.	The study demonstrated that cadexomer iodine reduces the total microbial load in biofilm-complicated DFUs, altering microbial composition, richness, and diversity. There was no statistically significant difference in microbial load reduction between the groups treated for two weeks (0.35 Log10) and six weeks (0.5 Log10, p=0.71). Furthermore, the duration of treatment did not affect microbial composition, richness, or diversity. Although topical antimicrobial agents impact microbial load, this did not translate into higher healing rates.
Clinical usefulness of quantifying microbial load from diabetic foot ulcers: a multicenter cohort study	Soldevila-Boixader et al., 2022 Spain	Multicenter, prospective cohort study	To evaluate whether the microbial load of DFUs can help predict outcomes.	Sixty-five diabetic patients, median age of 65 years, with DFU were included. Quantitative cultures of DFU biopsies were collected at the initial visit, classifying microbial loads as high (≥6 log - Colony Forming Units - CFU/mL) or low (<6 log CFU/mL). The responsible team diagnosed clinical infection in all patients and selected the most appropriate antibiotic therapy, following established guidelines. In the absence of osteomyelitis, treatment generally lasted two to three weeks. Outcomes were evaluated after six months, considering failure (persistence, new infection, or amputation) or healing (total or partial healing when the ulcer reduced > 50% of its initial size).	Of the 65 patients, 52 (80%) had long-standing DFU (≥4 weeks), with a high microbial load in 19 (29%). DFU infection occurred in 24 patients (37%), but was not always associated with a high microbial load, except in cases of shorter duration. Treatment failure was observed in 20 of 57 (35%) patients, with a high microbial load associated with worse outcomes (nine of 20 had a failure rate of 45%, adjusted OR 4.69; 95% CI, 1.22–18.09; p = 0.03), especially among those with long-standing DFU. In total, 65% of patients achieved cure, while 35% required minor amputation. Almost all patients received antibiotics during the six-month follow-up.
Application of compound Polymyxin B ointment in the treatment of chronic refractory wounds	Tang et al., 2022 China	Retrospective cohort study	To investigate the clinical efficacy of polymyxin B ointment in the treatment of refractory chronic wounds.	The study included 111 patients with refractory chronic wounds (defined as not healed for more than one month). All patients had controlled systemic infections and stable underlying disease, with a mean age of 61.32 years. Participants were divided into two groups: 45 in the experimental group, which received polymyxin B ointment, and 66 in the control group, which received silver sulfadiazine cream. After debridement, the treatments were applied and covered with sterile gauze, with dressing changes depending on the wound condition. Follow-up occurred throughout 21 days. Wounds included DFU, pressure injuries, infectious wounds, vascular ulcers, traumatic wounds, burns, and radiation ulcers. Healing, infection, and healing time were assessed using the Bates-Jensen Wound Assessment Tool (BWAT).	The results showed no significant difference in BWAT scores between the two groups at day 7 and day 14. However, at day 21, the experimental group that received polymyxin B ointment had a significantly lower BWAT score compared to the control group that used sulfadiazine (p < 0.05). Furthermore, healing time was significantly shorter in the experimental group. Complete debridement followed by application of polymyxin B ointment proved effective in reducing infection and accelerating the repair of refractory chronic wounds.

continue

Summary of selected studies

Study title	Author/Year/ Country	Type of study	Objective	Sample	Main results
Safety and performance evaluation of a next-generation antimicrobial dressing in patients with chronic venous leg ulcers	Harding et al., 2016 United Kingdom and Poland	Pre-market non-comparative controlled study	To investigate the safety and performance of the AQUACEL™ Ag+ dressing, which combines antibiofilm and antimicrobial agents, in the treatment of chronic wounds.	The sample consisted of 42 patients with venous leg ulcers showing signs of clinical infection, recruited from six centers in the United Kingdom and Poland. Patients aged 18 years or older were included, with ulcers lasting less than 24 months and measuring between 5 and 40 cm², in addition to meeting at least three of the five clinical signs of infection (pain between dressing changes, erythema/inflammation of the periulcer skin, edema, foul odor, and intense exudate). At the beginning of the study, the ulcers were classified into two categories: clinically infected, which required antibiotics, and non-clinically infected, which showed signs of infection but did not require antimicrobial treatment. Follow-up was conducted for up to eight weeks, during which patients underwent four weeks of treatment with the AQUACEL™ Ag+ dressing, followed by another four weeks with the AQUACEL™ dressing.	Of the 42 patients enrolled, 10 were considered clinically infected but did not receive antibiotics. At the end of the eight-week study, five patients (11.9%) had healed ulcers and 32 (76.2%) showed improvement. The mean reduction in ulcer area was 54.5%, with a 70.2% decrease in clinically infected ulcers. The pain reported by patients decreased significantly, from an average of 4.46 at baseline to 1.94 at week eight. The AQUACEL™ Ag+ dressing demonstrated an acceptable safety profile and substantial improvements in patients with venous leg ulcers, including wounds with signs of infection.
Clinical assessment of a biofilm-disrupting agent for the management of chronic wounds compared with standard of care: a therapeutic approach	Kim et al., 2018 USA	Prospective, randomized, and open-label clinical trial	To study the therapeutic efficacy of a biofilm-disrupting gel developed for the treatment of chronic wounds.	The study evaluated 43 patients with recalcitrant chronic wounds at two research centers over 16 weeks. Of these, 22 received the gel (experimental group: BlastX; Next Science, Jacksonville, FL) and 21 (control group: Neosporin + Pain Relief; Johnson & Johnson, New Brunswick, NJ) were treated with an antibiotic ointment. Wound areas were measured at weeks 0, 2, 4, 8, 12, and 16 using a camera. The primary outcome was the percentage reduction in wound area after 12 weeks.	The study revealed that the experimental biofilm-disrupting gel resulted in an average wound area reduction of 72% after 12 weeks, compared to only 15% in the control group, a statistically significant difference ($p < 0.01$). The wound closure rate was 52% in the experimental group, in contrast to 17% in the control group ($p < 0.01$). Furthermore, the healing rate in the experimental group was 2.44 times higher than in the control group. The use of the gel was considered safe.
Lights, fluorescence, action-influencing wound treatment plans including debridement of bacteria and biofilms	Jacob et al., 2023 USA	Retrospective study	To analyze how fluorescence imaging (FL-imaging) influences wound treatment planning by comparing treatment decisions before and after the use of this technology in a real clinical setting.	The sample consisted of 1,000 chronic wounds evaluated by clinicians at 211 facilities in 36 states of the United States of America (USA). Wound types included DFUs, venous ulcers, pressure injuries, among others. Data collection was systematic, with clinicians assessing wounds and proposing treatment plans, which were revised after using FL-imaging technology (FL-imaging: MolecuLight i:X or DX). FL-imaging technology uses violet light (405 nm) to illuminate wounds, causing their components to fluoresce in different colors. Green FL indicates skin structures, while red and cyan FL signal high bacterial loads. This technique allows for the identification of infections, assessment of wound severity, and more precise adjustment of the treatment plan.	FL-imaging technology identified elevated bacterial loads in 70.8% of the chronic wounds evaluated, while only 29.6% showed clinical signs of infection. Following the use of FL-imaging, treatment plans were altered in 528 wounds (53.3%), with interventions such as more extensive debridement (18.7%), a significant increase in prescriptions for topical therapies (37.7%) $p<0.0001$, and prescription of systemic antibiotics (47.3%) $p<0.0001$. These results suggest that FL-imaging improved the management of bacterial infections.
Evaluation of the use of antibiofilmogram technology in the clinical evolution of foot ulcers infected by Staphylococcus aureus in persons living with diabetes: a pilot study	Sotto et al., 2021 France	Multicenter, observational pilot study	To evaluate the efficacy of antibiofilmogram technology in the clinical evolution of *Staphylococcus aureus*-infected ulcers in diabetic patients.	The study involved 28 diabetic patients with a mean age of 61.2 years, all with foot ulcers infected by *Staphylococcus aureus*, in three clinics in France. Adults with chronic, slow-healing wounds and no antibiotic treatment in the last 14 days were included. To assess bacterial biofilm formation and antibiotic efficacy, the antibiofilm assay method was used, which is performed in steps: first, a sample of the bacteria is cultured to form a biofilm on a specific surface; then, different concentrations of antibiotics are applied to the biofilm. After an incubation period, bacterial viability is assessed, allowing the determination of the biofilm minimum inhibitory concentration (bMIC), which provides information on bacterial resistance and the efficacy of the antibiotics tested.	Antibiofilmogram technology was effective in identifying antibiotics against *Staphylococcus aureus* biofilms in patients with foot ulcers. The analysis revealed that 15 patients had concordant results between the antibiofilmogram analysis and the antibiogram, while 13 had discordant results. Patients in the concordant group showed significant clinical improvement, with 80% showing favorable wound evolution compared to 38.5% in the discordant group.

continue

Summary of selected studies

Study title	Author/Year/ Country	Type of study	Objective	Sample	Main results
Efficacy of a Ceratothoa Oestroidesolive oil extract in patients with chronic ulcers: a pilot study	Vitsos, A et al. 2019 Greece	Pilot study	To investigate whether olive oil extract of *C. oestroides*, in combination with antiseptics and/or antibiotics, promotes the healing of pressure injuries and venous ulcers in patients who have not responded to standard treatment.	Fourteen patients with 19 wounds (12 pressure injuries, six venous ulcers, and one mixed venous and arterial ulcer) aged between 40 and 97 years were included. Patients clinically assessed as unresponsive to healing agents (for 12 weeks) were treated for three months with an ointment containing *C. oestroides* extract combined with antibiotic and/or antiseptic agents chosen according to the type of bacterial infection. Treatment assessment was performed using BWAT criteria with the +WoundDesk and MOWA mobile applications.	After three months of treatment with olive oil extract of *C. oestroides*, there was an average 36% reduction in the BWAT score of the ulcers, with complete healing in five patients (one venous ulcer and four pressure injuries). Most wounds presented a polymicrobial profile, and the most common infections were caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The average BWAT score before treatment was 39.05, decreasing significantly after three months. Wound chronicity showed a negative correlation with healing, while the initial wound size did not influence the results.
Efficacy of a topical concentrated surfactant gel on microbial communities in non-healing diabetic foot ulcers with chronic biofilm infections: A proof-of-concept study	Malone et al 2021 Australia	Proof-of-concept study	To explore the effects of combining standard treatment (start of care - SOC) with the topical application of surfactant gel (Plurogel®, Medline Industries Inc) in non-healing DFU with chronic biofilm infections.	The study was conducted at a hospital in Australia and included 11 individuals over 18 years of age presenting with non-healing neuropathic or neuroischemic foot ulcers. Participants were recruited over 18 months and were eligible if they had DFU with a high suspicion of chronic infection without the need for systemic antibiotics. Standard treatment (start of care - SOC) consisted of weekly care by a podiatrist, debridement, cleaning, and dressing use. In addition, patients received a concentrated topical gel (Plurogel®, Medline Industries Inc) applied every two days for up to six weeks.	One patient was excluded due to acute infection, and biofilm was confirmed in 10 participants. The concentrated topical gel reduced the total microbial load in seven of the 10 patients, but three showed an increase. The mean microbial load was 6.4 Log10 at baseline, 6.1 Log10 at week three, and 6.0 Log10 at week six, with no statistically significant difference ($p = 0.63$). The main bacterial groups at baseline were *Corynebacterium sp.*, *Streptococcus sp.*, *Fusobacterium sp., Staphylococcus sp.*, and *Anaerococcus sp.* Beta diversity showed no significant differences ($R = -0.069$, $p = 0.883$), with changes in microbial composition varying among individuals. Some bacteria such as *Corynebacterium sp.* and *Streptococcus sp.* decreased, while *Staphylococcus sp., Finegoldia sp.*, and *Fusobacterium sp.* increased. Changes in alpha diversity were inconsistent and uncorrelated with total microbial load, with community diversity re-establishing itself at week six.

Abbreviation: DFU - Diabetic Foot Ulcers; DNA - Deoxyribonucleic Acid; PCR - Polymerase Chain Reaction; CFU - Colony Forming Units; BWAT - Bates-Jensen Wound Assessment Tool; USA - United States of America; bMIC - Biofilm Minimum Inhibitory Concentration; SOC - Start of Care.

Surfactant gel, silver sulfadiazine, and cadexomer iodine

The surfactant-based 1% silver sulfadiazine dressing is a widely used antibacterial for preventing wound infections. A study evaluated the efficacy of a novel surfactant-based biomaterial dressing with 1% silver sulfadiazine in patients with chronic wounds of both sexes, mean age of 73.5 years and multiple comorbidities at a tertiary outpatient wound care center. Patients were divided into two groups: group A (88 patients), who had previously tried treatments without success and were receiving standard treatment, and group B (138 patients), who started the new treatment. The results showed a cure rate of 67.4% of the total population, with significantly better rates in group B (72.7%), at a median of 12 weeks, compared to group A (59.5%), cured at a median of 17 weeks. The new dressing demonstrated efficacy in different types of wounds and age groups, in addition to a significant reduction in treatment costs. According to the authors, the improvement in the results of group B suggests the effectiveness of the rapid initiation of treatment with a surfactant-based dressing, promoting wound cleansing and an ideal environment for healing. However, further studies are needed to support this conclusion.[18]

Another study evaluated the efficacy of concentrated surfactant gel (Plurogel®) in combination with standard treatment in patients with non-healing diabetic foot ulcers (DFU) suspected of having chronic biofilm infections. Eleven patients were recruited from a hospital in Australia, with one patient excluded after developing an acute infection. The presence of biofilm was confirmed in all participants. The results showed that the gel application reduced the total microbial load in seven of the 10 patients, with an average reduction of 0.8 copies of Log10 16S. However, three patients showed an increase in microbial load. The average bacterial load for all patients was 6.4 Log10 at baseline, 6.1 Log10 at midpoint, and 6.0 Log10 at the end of treatment, with no statistically significant difference between time points. Regarding the composition and diversity of the microbial community, the five most common bacterial types in the samples before treatment were *Corynebacterium sp., Streptococcus sp., Fusobacterium sp., Staphylococcus sp.*, and *Anaerococcus sp.* Beta diversity analysis did not identify significant differences in microbial composition between baseline and the end of treatment, although individual changes did occur. While alpha diversity varied among patients - some showed increased and

others decreased richness and uniformity of sub-operational taxonomic units - by the end of treatment, levels generally returned to those similar to baseline. These changes in diversity were not directly related to changes in total microbial load, indicating transient and patient-specific alterations.[7]

One study evaluated the efficacy of two durations of topical antimicrobial therapy with cadexomer iodine in patients with DFU complicated by chronic biofilm infections. Eighteen patients completed the study without adverse events. Microbial loads in the two- and six-week treatment groups showed no significant differences (4.3 Log10 and 4.5 Log10, $p = 0.36$). However, there was an average reduction of 0.5 Log10 in microbial load in 14 of the patients, with $p = 0.04$, indicating statistical significance. DNA sequencing identified genera such as *Corynebacterium, Staphylococcus, Morganella*, and *Pseudomonas*, with changes in microbial composition after treatment. Regarding wound metrics, there was no significant difference in ulcer duration between the groups. At the end of the study, five of the eight patients in the two-week group were healed, compared with two of the 10 patients in the six-week group ($p = 0.145$). Significant improvements were observed in exudate, odor, and granulation tissue quality. The results suggest the effectiveness of cadexomer iodine therapy in reducing the microbial load in DFU, with benefits in wound metrics, although healing rates were not statistically significant.[7]

A separate study examined 34 participants with a mean age of 80 years. Local treatment methods included various ointments and dressings, with iodine ointment being the most frequently used (29.4%). Systemic antibiotics were administered to 26.5% of participants, and contamination of the ulcers by feces and urine was observed in 8.8% of cases. The results demonstrated that the use of iodine ointment correlated negatively with changes in the proportion of biofilm area (correlation coefficient = -0.42). Multivariate analysis indicated a significant association between iodine ointment use and biofilm area reduction ($\beta = -0.26$; $p = 0.003$). These findings suggest the medication's effectiveness in managing critically colonized pressure injuries, underscoring the importance of targeted local wound care.[11]

Polymyxin B, AQUACEL™ Ag+ and olive oil extract of *Ceratothoa oestroides*

Innovative treatments evaluating the efficacy of different agents have been studied as options in the healing of chronic wounds. A retrospective study analyzed data from 111 patients with refractory chronic wounds. The patients were divided into two groups: 45 received treatment with polymyxin B ointment, while 66 were treated with silver sulfadiazine. There was no significant difference in demographic characteristics or wound severity between the groups. Although there were no significant differences in Bates-Jensen Wound Assessment Tool (BWAT) scores at days 7 and 14, there was a significant improvement at day 21 for the experimental group, with a mean score of 21.33, compared to 23.41 in the control group ($p < 0.05$). Healing time was also significantly shorter in the polymyxin B group, with a mean of 48.18 days compared to 59.06 days in the silver sulfadiazine group ($p < 0.05$). Furthermore, no evident adverse effects were observed in either group.[19]

Another study aimed to investigate the safety and performance of AQUACEL™ Ag+, a wound dressing containing a combination of antibiofilm and antimicrobial agents. The AQUACEL™ Ag+ study involved 42 patients with chronic venous ulcers recruited from six centers in the UK and Poland. Among participants, five ulcers (11.9%) healed completely by the end of the study, while 24 patients (58.5%) showed marked improvement in their conditions. At the beginning of the study, 71.4% of the ulcers were deteriorating or not improving. After eight weeks of treatment, an average reduction of 54.5% in ulcer area was observed, and patients with clinically infected ulcers showed an even greater reduction of 70.2%. Patient pain was monitored in the study, with assessments throughout the treatment, as well as their comfort during dressing changes, indicating a positive experience. One patient discontinued treatment due to a serious adverse event unrelated to the dressing; a femur fracture. Results suggest that AQUACEL™ Ag+ is safe and effective in treating chronic venous ulcers, showing potential in the management of complex wounds.[20]

A recent study investigated if olive oil extract of *C. oestroides* combined with antiseptics and/or antibiotics improved the healing of pressure injuries and chronic venous ulcers in patients who did not respond to standard treatment. The study recruited 14 outpatients aged between 40 and 97 years. They presented with wounds that failed to heal after 12 weeks of standard care. Interventions included the application of an ointment based on olive oil extract of *C. oestroides* after wound cleansing. Assessments were performed every two weeks using the BWAT wound assessment tool to measure healing. Microbiological analyses revealed the presence of polymicrobial infections; *Pseudomonas aeruginosa* and *Staphylococcus spp.* were the most common pathogens. Antibiotic resistance was observed in some strains. After three months of treatment, BWAT scores showed a significant reduction, indicating improved healing, with complete cure in five patients. Pressure injuries and venous ulcers showed similar responses to treatment, with a decrease in BWAT scores, and healing was negatively correlated with wound chronicity. The results suggest that *C. oestroides*

extract may be a promising option for the treatment of chronic ulcers.[22]

Microbial load, biofilm-disrupting gel, fluorescence imaging, and antibiofilmogram

High bacterial loads in chronic wounds increase the risk of infection and complications.[1] Evaluating 65 diabetic patients (mean age 65 years) in three Spanish hospitals, a study used biopsies to determine if the microbial load of neuropathic or neuroischemic DFUs could predict treatment outcomes. The main results showed that 29% of patients presented a high microbial load (≥ 6 log CFU/mL), while 71% had a low load. The group with a high microbial load presented ulcers of shorter duration and a greater tendency to initial infection. Most samples were polymicrobial, with a predominance of gram-positive bacteria, especially *Staphylococcus aureus* in high counts. After six months, 65% of patients achieved healing, but high microbial load was identified as a significant predictive factor for treatment failure, with an odds ratio (OR) of 3.51. Patients with high load and long-standing ulcers had even more failures (63.6% vs. 28.5% in low load). After adjustments, high microbial load maintained its association with the failure rate (adjusted OR of 4.69). The findings suggest that microbial load is an important factor to consider in the management of DFUs.[17]

Another study investigated the efficacy of a biofilm-disrupting wound gel in the treatment of recalcitrant chronic wounds. The study was conducted at two sites: Mayo Clinic and River City Clinical Research (Florida, USA). The study enrolled 43 patients diagnosed with recalcitrant chronic wounds, all participants presented with one or more comorbidities, and 60% had diabetes. They were randomized into two groups: an experimental group, which used the wound gel (BlastX), and a control group that used a triple antibiotic ointment (Neosporin + Pain Relief). The treatment lasted 12 to 16 weeks, with multi-stage assessments throughout the period. After 12 weeks of treatment, the experimental group showed an average reduction in wound area of 72% ± 8%, significantly greater than the reduction observed in the control group ($p < 0.01$). Furthermore, 52% of patients in the experimental group achieved complete wound closure, compared to only 17% in the control group ($p < 0.01$). The results indicated that the experimental gel was more effective in promoting the healing of chronic wounds compared to standard treatment.[13]

Researchers analyzed how fluorescence imaging (FL-imaging) impacts wound treatment planning by comparing decisions before and after the use of this technology. A retrospective analysis of 1000 chronic wounds evaluated in 36 US states was performed. Wound types included DFUs, venous ulcers, pressure injuries, arterial ulcers, surgical wounds, and burn wounds. Clinicians from 211 facilities participated. Data were captured electronically during FL-imaging encounters, with initial wound assessment and treatment plan proposed by the clinicians. Fluorescence imaging was performed using specific devices, allowing visualization of bacterial loads. The results show the analysis of 990 wounds after excluding 10 due to lack of imaging results. Of these, 71.8% of the wounds showed signs of high bacterial loads. Clinicians altered their treatment plans for 53.3% of the wounds after visualization of FL-imaging, with significant changes in the antimicrobial approach: topical prescriptions increased by 37.7% and systemic antibiotic prescriptions increased by 47.3%. One example showed how FL-imaging indicated subsurface bacterial loads in a DFU, resulting in additional debridement and prescription of systemic antibiotics based on the new information. The authors concluded that FL-imaging had a significant impact on treatment decisions, especially in the antimicrobial approach, demonstrating its value in the management of chronic wounds.[23]

Another study evaluated the effectiveness of antibiofilmogram technology in the clinical evolution of *Staphylococcus aureus*-infected ulcers in diabetic patients. The study included 28 diabetic patients with a mean age of 61.2 years, recruited from three French clinics. Patients were assessed for the presence of diabetic foot infections and received antibiotic treatment for 14 days. Treatment effectiveness was monitored through clinical and bacteriological assessments, including antibiofilmogram analysis to examine biofilm formation and antibiotic susceptibility. The results identified the presence of *Staphylococcus aureus* in all patients at inclusion; infection was present in 25% of patients at day 14 and in 32.1% at day 45. The group with concordant results between antibiogram and antibiofilmogram showed significant clinical improvement (80.0% vs. 38.5%, $p = 0.0245$) and less exudation (0% vs. 30.8%, $p = 0.0282$) at day 14. At the end of treatment, 17 patients showed favorable wound healing, with concordance of antibiogram/ antibiofilmogram observed in patients with positive evolution, with a relative risk of 3.1 (95% CI: 1–9.2). The authors suggest that an antibiotic strategy with information on the action of antibiotics against biofilms may be a promising approach to improve healing outcomes in patients with DFU.[24]

The studies presented have significant limitations that should be considered. The small sample size[7,11,13,17,20,22,24] reduces the power to detect significant differences in cure rates.[7] Observational or uncontrolled studies make it difficult to determine causal relationships.[7,11,17,19,20,23,24] A study collecting biopsies at a single time point may have failed to capture the full microbial diversity. Furthermore, the choice of biopsies limits the capture of microorganisms in depth, and the

qPCR technique (quantitative polymerase chain reaction) does not distinguish viable from non-viable cells, compromising the interpretation of the results.[7]

One study showed a high average age of participants (80 years), which may impact the generalizability of the results.[11] Even though it is a multicenter study, the results obtained in reference hospitals may not be applicable to other contexts.[17] Another study was limited to reporting patient adherence without objective monitoring and did not match groups in relation to comorbidities, which complicated the interpretation of the results. Furthermore, the use of additional treatments made the analysis even more complex.[13]

Implications for clinical practice

Evidence indicates that innovative dressings, such as surfactants with silver sulfadiazine, are effective in healing chronic wounds, especially in patients with comorbidities. In addition, agents such as polymyxin B and AQUACEL™ Ag+ have demonstrated better results than standard treatments, highlighting the importance of targeted antimicrobial approaches. Olive oil extract of *C. oestroides* is also an option for those who do not respond to conventional therapies. Personalization of treatment, based on microbiological data and microbial load, is essential to optimize outcomes. Furthermore, the use of biofilm-disrupting gel significantly increased the healing of recalcitrant chronic wounds compared to the control group. The use of technologies, such as FL-imaging, can enhance the identification of infections and the selection of antibiotics, resulting in effective and targeted management. The speed of implementation of these approaches is crucial to improving healing rates and clinical outcomes for patients.

Future studies with larger cohorts are fundamental to enhance population representativeness and the generalizability of the findings. The implementation of rigorous experimental designs, such as randomized clinical trials, is essential to minimize biases and ensure internal validity. Furthermore, extending follow-up periods allows for the analysis of long-term effects, while diversifying recruitment strategies facilitates the inclusion of varied subgroups, promoting a more heterogeneous sample. In addition, all studies should assess and record the development of treatment-related adverse events.

This review presents important limitations that should be considered. The small sample sizes of the included studies compromise the generalizability of the findings. Methodological heterogeneity and lack of methodological rigor in some studies hinder direct comparisons and the synthesis of robust evidence.

The absence of standardization in biofilm detection techniques and in the definitions of clinical outcomes, associated with the scarcity of multicenter and long-term follow-up studies, limits the understanding of the sustained effectiveness of interventions in different contexts.

In accordance with the nature of narrative reviews, this study did not employ a systematic search protocol, which may introduce selection bias; however, the SANRA checklist was utilized to ensure quality. These limitations highlight the need for further research with greater methodological rigor, representative samples, and standardization of protocols to consolidate the evidence on the treatment of biofilms in chronic wounds.

CONCLUSION

This study demonstrates the effectiveness of innovative therapeutic approaches in the treatment of biofilms in chronic wounds. Surfactant-based dressings with silver sulfadiazine have promoted significant healing, especially when applied early. Ointments such as iodine and polymyxin B have also contributed to reducing biofilm and the healing time. The AQUACEL™ Ag+ dressing showed promising results in chronic venous ulcers, while olive oil extract of *C. oestroides* stood out as an effective alternative in patients refractory to conventional treatments.

Furthermore, microbial load, identified as a significant predictive factor for treatment failure, highlights the need for rigorous monitoring. Biofilm-disrupting gel proved effective, promoting superior healing compared to standard treatment. Fluorescence imaging positively impacted treatment decisions, allowing adjustments to antimicrobial therapy based on visible bacterial loads. Finally, antibiofilmogram technology proved promising in understanding bacterial resistance and optimizing treatment in *Staphylococcus aureus* infections.

On the other hand, surfactant gel shows contradictory results in the bacterial community, while antimicrobial therapies, such as cadexomer iodine, reduce the microbial load, but without statistically significant results in wound healing. Limitations of the studies, such as small sample sizes and lack of methodological rigor, indicate the need for further research. Large, randomized clinical trials are essential to validate these interventions and optimize the management of chronic wounds, improving patients' quality of life.

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