Kavanagh *et al. Plast Aesthet Res* 2024;11:43
DOI: 10.20517/2347-9264.2024.26

Plastic and Aesthetic Research

Review

Open Access

Exploring the efficacy of negative pressure wound therapy in the management of mycobacterium ulcerans wounds: a comprehensive literature review

Francene Kavanagh[1], Warren Rozen[1,2], Ishith Seth[2], Roberto Cuomo[3]

[1]Plastic Surgery Victoria, Peninsula Private Hospital, Langwarrin 3910, Victoria, Australia.
[2]Central Clinical School at Monash University, The Alfred Centre, Melbourne 3004, Victoria, Australia.
[3]Plastic Surgery Unit, Department of Medicine, Surgery and Neuroscience, University of Siena, Siena 53100, Italy.

Correspondence to: Prof. Roberto Cuomo, Plastic Surgery Unit, Department of Medicine, Surgery and Neuroscience, University of Siena, Mario Bracci Street, Siena 53100, Italy. E-mail: robertocuomo@outlook.com

How to cite this article: Kavanagh F, Rozen W, Seth I, Cuomo R. Exploring the efficacy of negative pressure wound therapy in the management of mycobacterium ulcerans wounds: a comprehensive literature review. *Plast Aesthet Res* 2024;11:43. https://dx.doi.org/10.20517/2347-9264.2024.26

Received: 21 Feb 2024 **First Decision:** 30 Jul 2024 **Revised:** 11 Aug 2024 **Accepted:** 20 Aug 2024 **Published:** 26 Aug 2024

Academic Editor: Hiroshi Mizuno **Copy Editor:** Dong-Li Li **Production Editor:** Dong-Li Li

Abstract

Mycobacterium ulcerans (M Ulcerans) infection leads to the debilitating Buruli ulcer (BU), characterized by necrotizing skin and soft tissue lesions. Conventional treatment primarily focuses on an antibiotic regimen, but wound management remains paramount to patient recovery. This literature review aims to evaluate the efficacy and benefits of Vacuum Assisted Dressing (VAC) in the treatment and management of BU wounds. A systematic literature search was undertaken using databases such as PubMed, Cinahl, Cochrane database, Joanna Briggs Institute, Medline, Internurse, Nursing & Allied Health database, and Scopus search from January 1995 to December 2023. The key search terms included "Mycobacterium ulcerans", OR "Buruli ulcer", AND "vacuum assisted dressing", "vacuum assisted therapy", "Vacuum Assisted Dressing", "negative pressure wound therapy", and "Negative Pressure Wound Therapy (NPWT)". The exclusion criteria were animal studies and studies not in the English language. The current literature emphasizes the importance of antibiotic treatment for BU and highlights the skin and soft tissue damage that results in open, infected wounds. However, there is a notable lack of quantitative data on the efficacy of NPWT for treating BU wounds. Early evidence indicates that NPWT might accelerate wound healing, decrease secondary infections, and enhance wound bed readiness for grafting or secondary healing. While more comprehensive quantitative studies are warranted, NPWT emerges as a promising adjunctive therapy in the holistic management of BU wounds, offering benefits that may improve patient outcomes and reduce morbidity.

Keywords: Vacuum-assisted closure, negative pressure wound therapy, Mycobacterium ulcerans, Buruli ulcer disease, wound

INTRODUCTION

The landscape of wound care has evolved dramatically, driven by advancements in medical technologies and a burgeoning demand to address the complexities of skin ulcers stemming from non-infectious origins, such as diabetes and peripheral arterial diseases, particularly in developed nations[1]. This surge in patient needs has catalyzed the growth of the wound management market, introducing innovative solutions aimed at enhancing healing processes[2]. Despite the potential for higher initial costs, these modern wound care techniques, including absorbent dressings and negative-pressure wound therapy, show promise in reducing overall treatment durations and, consequently, healthcare expenditures[3].

Among these advancements, the application of specific innovative methods like the HydroTac® absorbent dressing and the V.A.C. Therapy System® for negative-pressure wound therapy in managing Buruli ulcer (BU) wounds has reported encouraging outcomes[4]. These pioneering approaches not only signify progress in wound care but also highlight the necessity for further empirical studies to aggregate experiences and conduct cost-benefit analyses[5]. Such research is crucial in substantiating the long-term advantages of these treatments, paving the way for the development of cost-effective, field-appropriate wound management strategies[6].

Negative pressure wound therapy (NPWT) operates through a complex mechanism involving four primary actions upon initiation with an occlusive seal on the wound: macrodeformation, microdeformation, fluid removal, and alterations in the wound microenvironment [Figure 1][1,2]. When negative pressure is applied, the collapse of the sponge within the NPWT system induces macrostrain, drawing the wound edges closer and causing the wound bed's top layer to engage in microstrain[3]. This interaction between the foam's cellular structure and the wound bed facilitates the accelerated proliferation of granulation tissue, a process unique to NPWT. The therapy efficiently evacuates interstitial fluids, reduces edema, and enhances the delivery of growth factors and antibiotics to previously congested areas, thus fostering an optimal moist healing environment[4]. The application of NWPT creates an airtight seal over the wound, which facilitates continuous wound cleansing by effectively removing excess fluids and exudates. This process significantly reduces edema and enhances wound perfusion by alleviating the tension at the wound margins. The reduction in pressure around the wound edges improves microcirculation, thereby increasing oxygen and nutrient delivery to the wound site. This optimal microenvironment not only accelerates granulation tissue formation but also minimizes the risk of infection, supporting more efficient and effective wound healing[3]. The NPWT environment not only decreases the risk of infection but also stimulates local blood flow and granulation tissue formation more effectively with intermittent rather than continuous suction. The rationale behind this is that cellular adaptation to constant negative pressure might negate the beneficial elongation effects crucial for cell proliferation. Moreover, NPWT induces microdeformation at the cellular level, similar to principles observed in distraction osteogenesis and tissue expansion, where mechanical stress leads to cell proliferation [Table 1][1,2]. The application of local negative pressure and the physical properties of the NPWT foam material are instrumental in this cellular response, promoting neuropeptide production in keratinocytes, angiogenesis, and the release of growth factors. NPWT promotes the formation of granulation tissue under controlled moist conditions by preventing the accumulation of wound exudate. The system maintains a pathogen-impermeable barrier through its water vapor-permeable drape, which

Table 1. Proposed mechanism of action for negative pressure wound therapy

Mechanism of action	Description
Wound perfusion	NPWT enhances blood flow to the wound area, increasing oxygenation and nutrient supply, which are crucial for tissue repair and regeneration
Wound perfusion	By promoting blood flow and reducing edema, NPWT may increase the expression of growth factors, such as PDGF and VEGF, which are essential for the proliferation and migration of cells necessary for wound healing
Growth factor expression	NPWT causes changes in the wound shape by drawing the wound edges together, which helps reduce the wound area and promote the advancement of granulation tissue
Macrodeformation	The vacuum effect of NPWT at the wound surface may stimulate cellular processes by altering the microenvironment of the wound, encouraging cell stretching, division, and migration
Microdeformation	NPWT removes excess fluids, including exudates and potentially infectious materials, from the wound bed, thereby reducing edema and promoting a moist wound healing environment
Decrease wound exudate	NPWT removes excess fluids, including exudates and potentially infectious materials, from the wound bed, thereby reducing edema and promoting a moist wound healing environment
Bacterial concentration	By removing wound fluids, NPWT may also help reduce the bacterial load in the wound area, potentially decreasing the risk of infection and promoting a more sterile environment for wound healing

NPWT: Negative pressure wound therapy; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor.

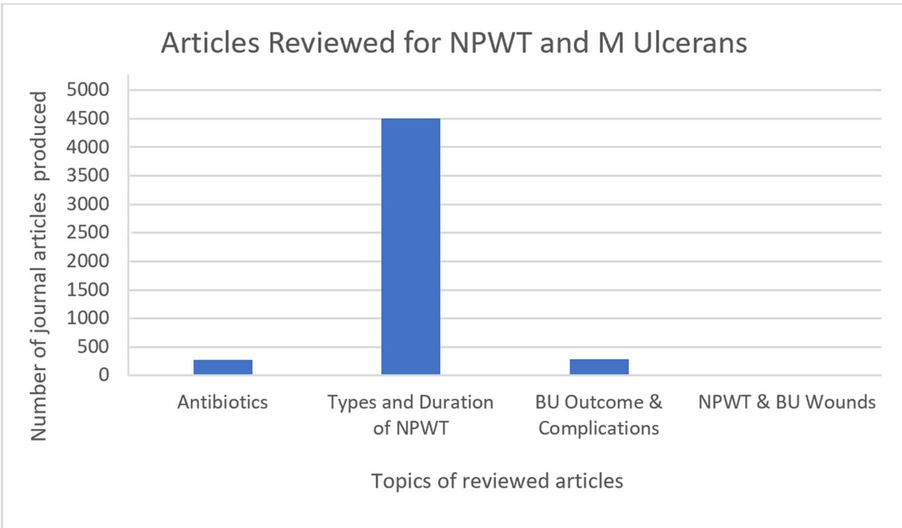

Figure 1. Articles reviewed for negative pressure wound therapy and mycobacterium ulcerans. NPWT: Negative pressure wound therapy; BU: Buruli ulcer.

prevents additional pathogen ingress while allowing excess moisture to escape. Although the wound environment is not entirely germ-free, the sealed system significantly reduces the risk of external contamination and helps create a more favorable environment for wound healing by supporting moisture balance and protecting against further infection[1,2].

The current standard treatment for BU primarily relies on antibiotic therapy, supplemented by surgical excision and conventional wound dressings to manage the extensive tissue damage. However, these traditional approaches often result in prolonged healing periods, increased rates of infection, and significant scarring. A critical gap in the treatment of BU is the need for more effective wound management strategies that can accelerate healing and reduce complications. NPWT offers a promising solution by promoting faster wound closure, enhancing the formation of granulation tissue, and decreasing bacterial contamination. This innovative therapy has the potential to significantly improve patient outcomes by reducing recovery time, minimizing the risk of secondary infections, and decreasing the extent of scarring, thereby representing a substantial advancement in the care of BU patients. The variability in wound management standards across healthcare providers and institutions underscores the imperative for standardized training and educational initiatives[7]. By harmonizing wound care practices, there is an opportunity to elevate the quality of patient care universally, ensuring that individuals suffering from BU and similar conditions receive optimal, evidence-based treatment[8]. This review aims to delve into the potential of NPWT as a cornerstone in the management of BU wounds, exploring its efficacy, cost-effectiveness, and role in the broader context of wound care innovation.

METHODOLOGY

PubMed, Cinahl, the Cochrane Database, the Joanna Briggs Institute, Internurse, the Nursing & Allied Health Database, and Scopus databases were searched from January 1995 to December 2023 for relevant studies that discuss the intersection of NPWT/VAC and BU. The search strategy was crafted to ensure the inclusion of a wide array of studies relevant to the objectives of this review. Key search terms used were: "Mycobacterium ulcerans" OR "Buruli ulcer" AND "vacuum assisted dressing", "vacuum assisted therapy", "Vacuum Assisted Dressing", "negative pressure wound therapy", and "NPWT". These terms were selected to uncover studies that specifically addressed the use of NPWT/VAC in the context of BU management. The search was refined to English-language publications to ensure the feasibility of comprehensive analysis and interpretation. The inclusion criteria were deliberately designed to encompass studies that evaluated the use of VAC or NPWT in conjunction with the treatment of Mycobacterium ulcerans (M Ulcerans) or BU. Exclusion criteria were applied to filter out studies that did not focus on the direct application of NPWT/VAC in BU treatment, non-English publications, and studies that did not present original research findings (e.g., commentaries, editorials, and reviews without primary data). The comprehensive literature review revealed 277 peer-reviewed articles examining the role of antibiotics in treating M Ulcerans infections [Figure 1][9].

The primary objective of this study is to evaluate the effectiveness of NPWT in accelerating wound healing and reducing infection rates in patients with BU. This includes a comparison of NPWT with traditional wound care methods to determine its superiority in managing the extensive tissue damage caused by M Ulcerans. The secondary objectives are to assess the impact of NPWT on reducing the need for surgical interventions, enhancing the readiness of wounds for grafting, and minimizing the overall treatment duration and hospital stay for BU patients. Additionally, the study aims to identify gaps in the existing literature on NPWT's application in BU treatment and provide recommendations for future research to further explore its clinical and cost-effectiveness in this context.

The systematic search process was conducted by two independent reviewers who followed a rigorous two-tiered approach. Initially, the reviewers screened titles and abstracts to identify studies that appeared to meet the predefined inclusion criteria. Studies that passed this preliminary screening underwent a detailed full-text review to confirm their eligibility. The reviewers assessed each study based on the inclusion and exclusion criteria established for this review, ensuring a high level of rigor in the selection process. In addition to the primary database search, the reviewers also examined the reference lists of all selected publications to identify any additional studies that may have been overlooked in the initial search.

RESULTS

Antibiotic therapy in M Ulcerans infection

These studies span a wide array of topics, including the critical evaluation of rifampicin-based combination antibiotic therapy. There is ongoing debate regarding the optimal duration of antibiotic treatment, comparing the traditional eight-week course to a potentially sufficient six-week regimen[10]. Additionally, discussions extend to the natural progression of BU wounds in the absence of immediate antibiotic intervention and the looming threat of antibiotic resistance in M. ulcerans strains[11].

NPWT and duration

The examination of NPWT yielded over four thousand peer-reviewed articles, with a significant focus on the technology and its applications. The literature delineates between NPWT systems powered by batteries and those that rely on electronic mechanisms, highlighting the operational differences and implications for patient mobility and wound exudate management. Battery-operated NPWT devices, while offering greater mobility due to their size and portability, exhibit limitations in exudate evacuation capacity[12]. Conversely, electronic NPWT devices are more adept at managing larger wounds with higher exudate levels but can restrict patient mobility due to their dependency on external power sources[13]. These studies predominantly address the application of NPWT in the management of diabetic foot ulcers and various limb wounds, illustrating NPWT's role in reducing surgical site infections and serving as a prophylactic measure for delayed primary abdominal wound closures [Figure 2][14]. The evidence consistently supports NPWT's effectiveness in treating both chronic and acute wounds, with a safe application duration extending beyond 4-5 days[15].

Comparative efficacy of NPWT

Compared with traditional dressing methods such as silver-impregnated and simple moist wound dressings, NPWT emerges as a superior option in terms of cost-effectiveness and labor intensity[16]. The analysis underscores NPWT's significant advantage in reducing infection rates across diverse wound types and locations, reaffirming its value as a cost-efficient and efficacious wound care strategy. The amassed literature indicates a robust endorsement of NPWT's utility in wound management, highlighting its economic and therapeutic benefits in a broad spectrum of clinical scenarios[17]. While NPWT systems may have a higher upfront cost compared to conventional dressings, their ability to enhance wound healing, reduce infection rates, and decrease the need for additional surgical interventions potentially offsets these initial expenses[16]. Traditional wound care often involves repetitive dressing changes, increased nursing time, and extended hospital stays, all of which contribute to higher overall treatment costs. In contrast, NPWT's efficiency in wound management can lead to shorter healing times, reduced hospitalization, and lower long-term costs[16]. Furthermore, the potential for NPWT to prepare wounds more effectively for grafting or secondary closure further underscores its cost-effectiveness, particularly in complex cases like BU, where extensive tissue necrosis is present. As NPWT minimizes the risk of secondary infections and promotes faster recovery, its application in BU treatment is not only clinically advantageous but also offers a promising cost-effective strategy, especially in settings where healthcare resources are constrained[17]. These factors collectively support the integration of NPWT into standard BU treatment protocols, necessitating further research to quantify its cost-benefit profile comprehensively.

BU, resulting from M Ulcerans infection, causes severe skin and subcutaneous tissue damage, often necessitating more than antibiotic therapy, such as surgical interventions or novel wound management methods like NPWT[18]. The disease's complexity is heightened by the mycolactone toxin produced by the bacterium, which destroys tissue and hinders immune responses, complicating treatment and vaccine development efforts. Although there are isolated reports, such as those by Murase *et al.*, showcasing the successful application of NPWT in BU treatment, these instances, while informative, provide limited evidence due to their anecdotal nature[9]. NPWT's mechanisms - exudate removal, moist environment maintenance, blood flow enhancement, and edema reduction - offer theoretical benefits for BU care. Yet, the scarcity of controlled clinical trials on NPWT's efficacy for BUs means its advantages are not conclusively established, particularly in comparison to standard care methods[19,20]. In summary, while

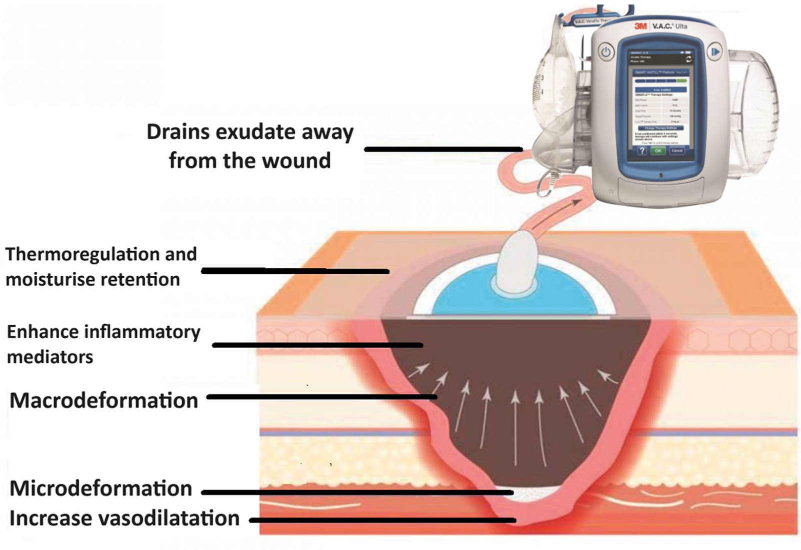

Figure 2. Mechanism of action of negative pressure wound therapy.

NPWT/VAC shows potential in managing BU wounds, evidenced by case reports, comprehensive research and clinical trials are needed to validate its effectiveness systematically[21]. Additionally, considerations for its application in low-resource settings, where BU predominantly occurs, are essential for broadening access to this advanced wound care technology[22].

DISCUSSION

The management of BU caused by M Ulcerans necessitates a comprehensive approach due to the extensive necrosis and damage to skin and soft tissues associated with the infection. Over recent decades, wound management has seen significant advancements, particularly with the development of NPWT technologies[23]. These innovations, introduced over the past fifteen years, utilize negative pressure to manage wound moisture and promote tissue granulation, proving especially beneficial for open and infected wounds[23].

The use of NPWT for the treatment of BU is relatively underexplored in the literature, with only a few case reports and small studies available. However, the current body of research is limited in scope and mostly anecdotal, highlighting a significant gap in the evidence base. Despite the clear applicability of NPWT to the open and infected wounds caused by M. ulcerans, there remains a notable absence of quantitative research confirming its effectiveness specifically for BU wound care. The theoretical alignment of NPWT's mechanisms with the needs of BU wound management is evident. However, the lack of rigorous comparative studies between standard wound care practices and NPWT in the context of BU limits the ability to definitively advocate for NPWT's superiority in these cases.

The evolution of wound management has significantly benefited from technological advances and the introduction of specialized dressings like NPWT. For conditions such as BU, where the pathogen induces necrotic, open wounds, incorporating advanced wound care strategies into the treatment plan is crucial. While the efficacy of NPWT for general open and infected wounds is well-established, the specific benefits for BU wounds require further quantitative analysis to ensure evidence-based practice in their management.

A comprehensive quantitative study comparing NPWT to traditional wound dressing methods in the treatment of BU wounds is recommended. Such research would provide the necessary data to support the integration of NPWT into BU treatment protocols, potentially improving patient outcomes through faster healing times and more efficient wound management. The call for evidence-based practices in healthcare, including wound management following M. ulcerans infection, highlights the urgent need for specific research into NPWT's application for BU. As M. ulcerans emerges as a significant pathogen, particularly in regions like Southeast Australia, the development of evidence-based treatment protocols for BU wounds becomes imperative. Establishing robust data on NPWT's efficacy will not only support clinical decision making but also enhance the overall quality of care for individuals affected by this debilitating condition.

To close the gaps in the current understanding of NPWT for BU treatment, future research should prioritize the design of randomized controlled trials and large-scale observational studies. RCTs are needed to provide high-quality evidence on the efficacy and safety of NPWT compared to standard wound care practices in BU patients. These trials should focus on key outcomes such as wound healing rates, infection control, and patient quality of life. Additionally, large-scale observational studies would be valuable in assessing the long-term benefits and cost-effectiveness of NPWT in real-world clinical settings, particularly in low-resource environments where BU is most prevalent.

CONCLUSION

The potential of NPWT to improve patient outcomes in BU cases is significant, suggesting a promising avenue for enhancing wound care and recovery. This study highlights the critical gap in the current literature regarding the specific application of NPWT in the treatment of BU. However, the absence of robust clinical trials and comparative studies leaves healthcare providers without a solid evidence base to guide the integration of NPWT into standard BU treatment protocols. The recommendation for future research is clear: a rigorous investigation involving controlled trials and comparative analyses is essential to establish the efficacy, cost-effectiveness, and practicality of NPWT in BU wound management.

DECLARATIONS

Authors' contributions

Involved in obtaining patients' data and writing and critically reviewing the manuscript: Kavanagh F, Rozen W, Seth I, Cuomo R

All authors approved the final manuscript.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Bretzel G, Beissner M. PCR detection of Mycobacterium ulcerans-significance for clinical practice and epidemiology. *Expert Rev Mol Diagn* 2018;18:1063-74. DOI PubMed
2. Cozza V, Pepe G, Cintoni M, et al. Vacuum-assisted closure (VAC®) systems and microbiological isolation of infected wounds. *World J Emerg Surg* 2018;13:53. DOI PubMed PMC
3. Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014;51:301-31. DOI PubMed
4. Yoo JY, Kim JH, Kim JS, Kim HL, Ki JS. Clinical nurses' beliefs, knowledge, organizational readiness and level of implementation of evidence-based practice: The first step to creating an evidence-based practice culture. *PLoS One* 2019;14:e0226742. DOI PubMed PMC
5. Janssen AHJ, Mommers EHH, Notter J, de Vries Reilingh TS, Wegdam JA. Negative pressure wound therapy versus standard wound care on quality of life: a systematic review. *J Wound Care* 2016;25:154-9. DOI PubMed
6. Loftus MJ, Gates RJ, Crouch S, Sutton B, Johnson PD. A non-healing ulcer in a healthy young woman. *Aust Fam Physician* 2017;46:855-6. PubMed
7. Moore K. VAC therapy: interactions in the healing process. Available from: https://wounds-uk.com/wp-content/uploads/sites/2/2023/02/content_9001.pdf. [Last accessed on 22 Aug 2024].
8. Muleta AJ, Lappan R, Stinear TP, Greening C. Understanding the transmission of Mycobacterium ulcerans: a step towards controlling Buruli ulcer. *PLoS Negl Trop Dis* 2021;15:e0009678. DOI PubMed PMC
9. Murase C, Kono M, Nakanaga K, Ishii N, Akiyama M. Buruli ulcer successfully treated with negative-pressure wound therapy. *JAMA Dermatol* 2015;151:1137-9. DOI PubMed
10. O'Brien DP, Friedman ND, Cowan R, Walton A, Athan E. Six vs eight weeks of antibiotics for small mycobacterium ulcerans lesions in australian patients. *Clin Infect Dis* 2020;70:1993-7. DOI PubMed
11. O'Brien DP, Jenkin G, Buntine J, et al. Treatment and prevention of Mycobacterium ulcerans infection (Buruli ulcer) in Australia: guideline update. *Med J Aust* 2014;200:267-70. DOI PubMed
12. Pittet LF, Tebruegge M, Dutta B, et al; BCG Immune Response Study (BIRS) group. Mycobacterium ulcerans-specific immune response after immunisation with bacillus Calmette-Guérin (BCG) vaccine. *Vaccine* 2021;39:652-7. DOI PubMed
13. Pluschke G, Röltgen K. Mycobacterium ulcerans: methods and protocols. New York, USA: Humana Press; 2022. DOI
14. Saaiq M. , Hameed-Ud-Din, Khan M I, Chaudhery SM. Vacuum-assisted closure therapy as a pre-treatment for split thickness skin grafts. *J Coll Physicians Surg Pak* 2010;20:675-9. PubMed
15. Sizaire V, Nackers F, Comte E, Portaels F. Mycobacterium ulcerans infection: control, diagnosis, and treatment. *Lancet Infect Dis* 2006;6:288-96. DOI PubMed
16. Suzuki K, Luo Y, Miyamoto Y, et al. Buruli Ulcer in Japan. In: Pluschke G, Röltgen K, editors. Buruli ulcer. Cham: Springer; 2019. pp. 87-105. DOI
17. Tai AYC, Athan E, Friedman ND, Hughes A, Walton A, O'Brien DP. Increased severity and spread of mycobacterium ulcerans, Southeastern Australia. *Emerg Infect Dis* 2018;24:58-64. DOI PubMed PMC
18. Van Der Werf TS, Barogui YT, Converse PJ, Phillips RO, Stienstra Y. Pharmacologic management of *Mycobacterium ulcerans* infection. *Expert Rev Clin Pharmacol* 2020;13:391-401. DOI PubMed PMC
19. Velding K, Klis SA, Abass KM, van der Werf TS, Stienstra Y. The application of modern dressings to Buruli ulcers: results from a pilot implementation project in Ghana. *Am J Trop Med Hyg* 2016;95:60-2. DOI PubMed PMC
20. Yotsu RR, Richardson M, Ishii N. Drugs for treating Buruli ulcer (Mycobacterium ulcerans disease). *Cochrane Database Syst Rev* 2018;8:CD012118. DOI PubMed PMC
21. Xu S, Xiao X, Chen J. Stretchable fiber strain sensors for wearable biomonitoring. *Natl Sci Rev* 2024;11:nwae173. DOI PubMed PMC
22. Johnson PDR, Azuolas J, Lavender CJ, et al. Mycobacterium ulcerans in mosquitoes captured during outbreak of Buruli ulcer, southeastern Australia. *Emerg Infect Dis* 2007;13:1653-60. DOI PubMed PMC
23. Seth I, Gibson D, Lim B, et al. Advancements, applications, and safety of negative pressure wound therapy: a comprehensive review of its impact on wound outcomes. *Plast Aesthet Res* 2024;11:29. DOI