



## Case report

# Innovative biochemisurgical treatment for stabilisation of an end-stage chronic wound in a complex vascular compromised patient

A. Algharib<sup>a,\*</sup>, L.M.C. van Dortmont<sup>a</sup>, M.G.R. Hendrix<sup>b</sup>, S. Riedel<sup>a</sup>, R. Möller<sup>a</sup>, G.G. Koning<sup>a</sup>

<sup>a</sup> Department of Vascular & Endovascular Surgery, EUREGIO Hospital, Albert-Schweitzer-Straße 10, 48527 Nordhorn, Niedersachsen, Germany

<sup>b</sup> Department of Medical Microbiology, EUREGIO Hospital, Albert-Schweitzer-Straße 10, 48527 Nordhorn, Niedersachsen, Germany

## ARTICLE INFO

## Keywords:

Biochemical  
Debridement  
Chronic  
Wound  
Ulcer  
Vascular  
Diabetic  
Foot  
Leg  
Desiccating agent A  
Debrichem  
Topical desiccation agent-A (TDA)

## ABSTRACT

**Introduction:** Treating advanced peripheral arterial occlusive disease (e.g. PAOD IV) poses a significant challenge, as conventional treatments quite often fall short at this stage. However, a range of interventions can be considered to postpone amputation. This study presents an example of advanced stage of Peripheral Artery Occlusive Disease (PAOD) stage IV, encompassing a history of a high thigh amputation on the left side, coupled with pronounced wound healing disorders.

**Presentation of case:** Our patient, 55 years old, smoker and ASA Class III is in a left sided above-the knee-amputation situation. He presented to our outpatient clinic with blistering in the stump area, caused by non-proportionate pressure from the prosthesis. With an emerging septic course and advanced peripheral arterial occlusive disease (PAOD) at Fontaine class IV, revascularization was unfeasible in the left iliac artery axis and groin arteries. Additionally, a stage PAOD IV presents itself with poorly healing wounds on the right side which our patient still uses to support his transfers in and out bed and his wheelchair. Multiple surgical stump revisions and femur shortenings and diverse wound treatments were performed all were unsatisfying for patient and practitioners. We introduced a novel biochemisurgical treatment in our teaching hospital.

**Discussion:** Desiccating-agent-A is an innovative dehydrating agent with potent desiccating characteristics upon application to organic substances. Its formulation involves blending 83% methane sulfonic acid with proton acceptors and dimethyl sulfoxide, as outlined in patent application. The case description results in an illustrated follow up period of 16 months and is presented in line with the recommendations of the consensus-based surgical case reporting guideline development.

**Conclusion:** The goal of achieving a secondary healing trend is to establish stability within the wound area or achieve complete healing. This endeavor becomes particularly intricate when severe blood circulation compromise exists. Nonetheless, progress in wound treatment measures has made it feasible to achieve this aim by fostering the formation of dry and clean necrotic tissue. This dry and clean wound is now manageable in a patient's home situation, allowing for effective care and a better chance at preventing further severe complications.

## 1. Introduction

Chronic skin wounds pose a substantial global health concern, accompanied by significant economic implications. The prevalence of these wounds within the general population approximates 1.5 %, with a higher incidence among the elderly [1]. The interplay of risk factors, including advanced age and the growing occurrence of conditions like diabetes even among younger individuals, foretells an escalation in chronic skin wounds [2]. Within specific populations, such as diabetic

patients, the prevalence of chronic ulcers varies significantly across regions. Rates range from 1.5 % in Australia to 16.6 % in Belgium, with North America experiencing an intermediate level [1]. The concerning prevalence of chronic wounds among diabetic patients, highlights the urgency of effective interventions. Chronic wounds are characterized by their failure to heal or reduce in size within a designated time frame of 4 to 12 weeks for this classification [2,3]. Successful wound healing is a composite outcome measure influenced by multiple factors, including wound dimensions, patient health, medication, and treatments.

\* Corresponding author at: EUREGIO Hospital, Department of Vascular & Endovascular Surgery, Albert-Schweitzer-Straße 10, 48527 Nordhorn, Niedersachsen, Germany.

E-mail address: [Ahmed.Algharib@Euregio-klinik.de](mailto:Ahmed.Algharib@Euregio-klinik.de) (A. Algharib).

<https://doi.org/10.1016/j.ijscr.2023.109103>

Received 20 September 2023; Received in revised form 26 November 2023; Accepted 2 December 2023

Available online 13 December 2023

2210-2612/© 2023 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The road to healing chronic wounds is marked by a varying timeline, extending from 6 weeks to over more than a year. This duration encompasses wounds treated at specialized wound care centers, exemplifying the complexities of wound healing. Factors such as wound size, patient health, and treatment modalities contribute to this extended timeframe [2,3].

While chronic wounds can stem from different etiologies, they often share common mechanisms that impede the healing process. Excessive inflammatory cells, cytokines, proteases, and persistent microbial burdens, often compounded by drug-resistant biofilms, serve as critical impediments to wound healing. Chronic wound healing necessitates the sequential progression through stages, including inflammation, neo-vascular growth, and cellular proliferation. Prolonged inflammation, characterized by the persistence of inflammatory mediators, pro-inflammatory macrophages, and neutrophils, hinders the advancement through these stages [4]. This obstruction contributes to the development and persistence of chronic wounds.

Current methods for managing chronic wounds typically involve surgical debridement to eliminate nonvital materials, using additionally specific wound dressing such as negative pressure therapy (VAC), being costly and slowly effective. However, this approach presents logistical and cost challenges. Researchers are now exploring nonsurgical options that can effectively restart the wound healing process [5].

Researchers have developed a novel hygroscopic gel named “Desiccating-agent-A” [5]. This gel contains 83% methane sulfonic acid, dry proton acceptors, and dimethyl sulfoxide as a biofilm penetration enhancer [2,5]. Bacteria, and particularly the presence of biofilms, also play a role in chronicity [6]. They contribute to the hyperinflammatory environment [7–13] and have a negative impact on the wound healing process [14]. In one study, biofilm structures were identified in approximately 80 % of samples (biopsies) collected from hard-to-heal skin lesions [9].

Biofilms have enhanced tolerance to antibiotics and antiseptics, as well as to host defence mechanisms [7,10,12]. Therefore, they are difficult to treat with solely (antibiotic or antiseptic) medication. Similarly, necrosis, containing among other components dead tissues and microorganisms, is known to hamper healing [13].

Consequently, the problem of biofilms and necrosis needs to be addressed as an essential step in getting a wound or ulcer to heal [6] as is reflected in different treatment modalities and protocols [8,9].

Regular and rigorous debridement is the preferred method of removing biofilm and necrosis [8,12].

Diverse methods of debridement can be used and include (hydro) surgical, biological, biosurgical and enzymatic techniques, as well as negative pressure wound therapy (NPWT) and other interventions. All of these methods come with their own benefits and drawbacks, such as slow activity (enzymes and autolysis) [10] or the requirement of specific expertise at a high cost (surgical excision) [1].

A new compound, a topical desiccation agent-A (TDA) has been designed to overcome a number of the disadvantages of more traditional debriding agents. The working mechanism is based on the rapid desiccating properties of certain acids. Its efficacy was first described in the treatment of acute periodontal abscesses [7,10]. TDA is an active gel containing an acidic species with a potent hygroscopic action [5] which, when in contact with microorganisms and necrosis, leads to swift desiccation and oxidation. This, in turn, causes denaturation of the proteins in bacteria, yeasts and viruses, as well as of the extracellular matrix of biofilms and necrotic tissues. This working mechanism will also harm viable cells and, therefore, TDA should be used within its indications and for a brief period [5].

Basic cleaning of the wound and the periwound skin is followed by the application of TDA over the lesion and about 1 cm of the periwound skin. After 60 s, the agent is diluted and removed by rinsing with sterile water or saline. The stratum corneum has a substantially lower water content than the tissues beneath it and, therefore, is not, or is only minimally, affected when exposed to TDA for a short period [5].

**Table 1**

Laboratory findings at moment of presentation in the emergency room.

Test	Value	International reference value
C-reactive protein (CRP)	300	<5 mg/L
Hemoglobin (Hb)	7.0	8.5–11.0 mmol/L
Red bloodcell count	3.7	4.3–6.0 × 10 <sup>12</sup> /L
White bloodcell count	14.6	4.0–10.0 × 10 <sup>9</sup> /L
Trombocytes	369	150–400 × 10 <sup>9</sup> /L
Sodium	137	135–145 mmol/L
Potassium	4.2	3.5–5.0 mmol/L
Creatinine	58	50–110 μmol/L
Estimated glomerular filtration rate	116	>60 mL/min
Ureum	4.0	2.5–7.5 mmol/L

The desiccation effect is virtually immediate; tissues denature, precipitate and coagulate together, and tend to rapidly separate from the underlying surface. There is no specific requirement for dressings or other interventions after application of TDA—these are used at the physician's discretion.

A known side-effect of the application of this type of material is a short-lasting pain sensation during and briefly after the application, which can be prevented by pretreatment of the wound bed with some form of anesthesia. As we did under general anesthesia in this case.

The primary goal of using TDA is the rapid elimination of biofilm and necrosis, thus reducing the chance of infection and initiating the ‘rebuilding’ part of the healing process, by creating a wound bed that can granulate.

We introduced this biochemisurgical treatment with TDA in our teaching hospital to stabilize the difficult wound as presented in the case. This report is written in line with the recommendations of the consensus-based surgical case reporting guideline development (SCARE guidelines) [15].

## 2. Presentation of case

Our patient, a 55-year-old male with vascular compromise and a history of diabetes mellitus, falls under ASA classification III, indicating moderate to severe systemic disease. Unfortunately he came to hospital after a huge patient-delay (weeks). He has a history of multiple operations, including an upper left leg amputation in another hospital, and wears a prosthesis on his left leg. Upon presentation at our outpatient clinic, his condition was notably poor, exhibiting pre-sepsis signs. The patient, who is a smoker with over 30 pack-years, falls under ASA-Class-III (American Society of Anesthesiologists). All baseline characteristics of the patient are presented in Table 1, the anemia was corrected during admission.

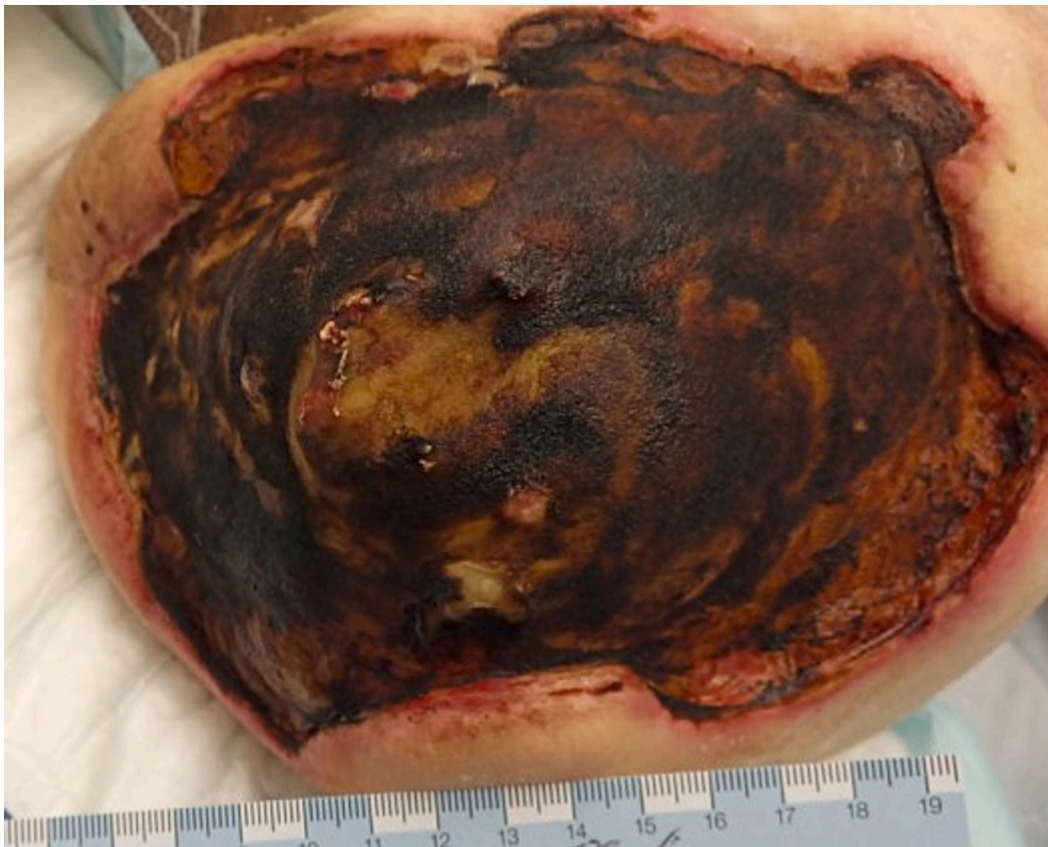
His current state involved a left-sided post-upper-left-leg-amputation scenario. The reason for his visit was due to blistering around the stump area, attributed to a non-proportionate pressure from the prosthesis which is a well known risk factor for developing a non healing ulcer. After wound cultures were taken and medical microbiological consultation, we started with antibiotics (Pipracilline/Tazobactam, 4,5 g 3 times daily) next to immediate required surgical debridement of the wound surface. Concurrently, he displayed signs of an emerging septic condition alongside advanced peripheral arterial occlusive disease (PAOD) classified as Fontaine class IV [16]. Unfortunately, revascularization options were completely deemed unfeasible for the left iliac artery axis and groin arteries. On the left side all main arteries were closed and perfusion was only supplied by collaterals. No landing zone could be identified (meaning a complete occlusion of all outflow/inflow possibilities). Previous attempts at multiple stump shortenings and various wound treatments yielded unsatisfactory results for both the patient and the medical team. We tried successively: open wound treatments, vacuum therapy (NPWT), grups therapy, fish skin application, split skin graft, hyperbaric-O<sub>2</sub> therapy in Münster and Düsseldorf and nothing succeeded in any form. The main goal of reaching a certain stabilized



Fig. 1. The left sided infected stump area, pus and open wound, on the day of admission.



Fig. 2. Picture after 2 months, and after multiple revisions and attempts to close the chronic wound, coming to a chronic end-stage phase now.



**Fig. 3.** Result 5 days after treatment with desiccating agent A (TDA), now the wound is in a stable and dry state for home care.

phase for these patients may contribute to quality of life outside the hospital. Main issue were the very painful daily changes of regular wound dressings. So we had to do something for this patient in a way to stabilize the wound surface into a dry surface. Causing no pain anymore during the changing of the wound dress.

Furthermore, we have included visual documentation with three accompanying photos: [Fig. 1](#) showcases the initial clinical presentation of the stump area; [Fig. 2](#) depicts the progression of the wound with visible blistering and signs of infection; and [Fig. 3](#) highlights the response to localized biochemical wound treatment using TDA (Debrichem, DEBx, Rotterdam, the Netherlands [1,5]) showcasing the evolution towards stable wound healing. Additionally, the timeline of events and interventions can be referred to in [Fig. 4](#), which provides a comprehensive overview of the patient's journey.

In an effort to address this challenging situation, we introduced a novel biochemisurgical treatment at our teaching hospital. The Instructions for Use (IFU) stipulated that Desiccating-agent-A (TDA) should be used for up to 1 min which we applied so during our first treatment in operating room (OR) circumstances [5]. Following this IFU, the initial treatment was carried out. However, to optimize the treatment conditions as much as possible, we opted to repeat this biochemisurgical intervention in the OR after a span of 14 days. This approach aimed to ensure the most favorable circumstances for the procedure. The ASA classification of III underscores the complexity of his medical history and emphasizes the need for a tailored approach to his care.

### 3. Discussion

Cases of advanced peripheral arterial occlusive disease (PAOD), particularly when classified as Fontaine class IV and accompanied by poorly healing wounds, often present significant challenges in terms of

treatment [1]. This is especially true when revascularization options have been exhausted. The complexities of managing such cases are extensively documented in the existing literature such as Cogo et al. 2020 and Hermans et al. 2022 [4,5]. Therefore, all treatment-steps in our approach were of multidisciplinary character. When confronted with these intricate scenarios, the decision to pursue secondary amputation, such as hip disarticulation, introduces considerable risk to the patient's life and must be weighed meticulously. In our case there was not enough vital skin for a safe and solid hip exarticulation ([Figs. 1–3](#)).

In certain instances, an alternative approach that focuses on localized wound treatment with TDA may offer a more viable strategy. Recent studies have drawn attention to the potential efficacy of TDA in facilitating wound healing and managing infections, particularly in cases resembling that of our patient. The primary objective of this approach is to achieve stable wound healing characterized by the presence of dry necrotic tissue within the wound area. This outcome can significantly enhance the wound's resistance against infections and potential pathogens [4,5,17].

Aligning with the principles outlined in wound care guidelines proposed by leading vascular associations, our strategy seeks to create an environment conducive to the formation of healthy tissue and hinder the progression of infection. By fostering the growth of dry and clean necrotic tissue, the wound becomes more manageable, even within the patient's home setting. This transformation, in turn, bolsters the overall effectiveness of wound care, mitigates risks associated with persistent infections, and improves the patient's quality of life (or health related quality of life). The success of such an approach, however, hinges on the collaborative efforts of a multidisciplinary team. In cases of advanced PAOD and poorly healing wounds, the involvement of various specialists is crucial. Wound specialists and wound nurses bring their expertise in wound assessment and management, while microbiologists contribute insights into infection control strategies. Rehabilitation experts play a

05.10.1967	•Patient born
19.04.2022	•Admission due to wound infection
09.05.2022	•Re-amputation (revision) with Diagnostic Subtraction Angiography (no vascular interventions possible at all)
23.05.2022	•Revision of the wound
29.06.2022	•Revision of the wound with split skin graft (autologous)
13.07.2022	•Patient discharged from hospital and further follow up at outpatient clinic
03.08.2022	•Re-admission due to wound infection
10.08.2022	•No other solutions then grupss-therapie
24.08.2022	•Revision of the wound and Hyperbaric Oxygen Therapy (Münster)
02.10.2022	•Revision of the wound with vacuum therapy (Negative Pressure)
20.10.2022	•Second Hyperbaric Oxygen Therapy (Düsseldorf)
01.12.2022	•further follow up at outpatient clinic
09.01.2023	•Re-admission due to wound infection
30.01.2023	•Revision of the wound with vacuum therapy
13.02.2023	•Revision of the wound with vacuum therapy
08.03.2023	•Revision of the wound with platelet enriched plasma-therapy in the wound surface
01.04.2023	•Discharge of the patient and further follow up at outpatient clinic
20.06.2023	•Re-admission due to wound infection and revision of the wound
30.06.2023	•Revision of the wound with first application with desiccating agent-A and again vacuum therapy
04.07.2023	•Revision of the wound with second application with desiccating agent-A (WITHOUT vacuum therapy)
13.07.2023	•Discharge of the patient and further follow up at outpatient clinic
22.08.2023	•Re-admission of the patient
25.08.2023	•Revision of the wound with third application with desiccating agent-A (WITHOUT vacuum therapy)
29.08.2023	•Patient discharged from hospital and further follow up at outpatient clinic, presently a dry and stable wound situation

Fig. 4. Time line of the patient in the case report.

pivotal role in optimizing the patient's overall functional recovery, and medical prosthesis experts ensure the appropriate fit and functionality of prosthetic devices.

Moreover, adding to the multidisciplinary team the important factor of dedicated anesthesiologists providing customized locoregional anesthesia tailored to the patient's unique medical profile, enhancing procedural outcomes and postoperative comfort, should, in our opinion, be taken into account. The vascular and endovascular optimization necessitates the skills of experienced vascular and certified endovascular surgeons who can navigate complex vascular issues, ensuring the best possible outcomes [18].

In line with all necessary steps and stages of innovations in surgical

Health Care (“the early steps”, “innovation”, “development”, “early dispersion & exploration” and “assessment” [19]) this innovative chronic wound treatment with TDA is currently between stage 2b and stage three [19]. Additional research is necessary to gain more data about this treatment. The available level of evidence for this first evaluation ( $n = 1$ ) is, presently at best, level-5 for this first report [20], our results should therefore be interpreted cautiously!

Next to the clinical experience with TDA, a decent cost effective analyses should be taken into account and this requires more investigation after the 3rd stage [19]. Such an analyses could be, for example, according to Brazier and should consist at least two scenarios: a hospital- and an analyses from societal perspective [21]. Moreover, factors

critical and none-critical for decision making should be evaluated in a later stage together with the patients. To assess if this treatment really contributes to a better health status or to improvement in quality of life, a patient centered evaluation and verification of patient reported outcomes should be performed [22].

In conclusion, the challenges posed by advanced PAOD and non-healing wounds are substantial and demand innovative approaches to treatment. The localized wound treatment strategy utilizing TDA holds promise in promoting stable wound healing and reducing the burden of infections. The successful implementation of such an approach underscores the critical importance of a well-coordinated multidisciplinary team that draws upon the expertise of various medical disciplines. This collaborative effort, which encompasses wound specialists, wound nurses, microbiologists, rehabilitation experts, medical prosthesis specialists, anesthesiologists, and vascular and endovascular surgeons, ensures comprehensive care that is tailored to the patient's unique needs. As we move forward, ongoing research and collaboration between medical disciplines will continue to refine our understanding and management of these complex cases, ultimately enhancing patient outcomes and quality of life.

#### Guarantor

A. Algharib, MD, Vascular surgeon  
G.G. Koning, MD, PhD, FEBVS, Vascular surgeon  
Euregio Hospital, Nordhorn, Germany

#### Conflict of interests, funding, ethical statement and informed consent

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. No funding for this study. Medical Ethical permission for this case report was not required after consultation of the Ärztekammer, Hannover, Germany. Our patient gave his full permission to use data and photographs for a case report and education.

#### CRedit authorship contribution statement

AA: writing manuscript.  
LvD: co-writing and critical reviewer manuscript.  
RH: reviewer manuscript, contribution to antibiotics paragraph.  
SR: co-writing and expertise in describing and photography of the wound.  
RM: co-writing and critical reviewing.  
GGK: co-writing, critical reviewing, supervision of treatment and preparing manuscript.

#### Declaration of competing interest

None.

#### References

- [1] J.F. Guest, V. Deanesi, A. Segalla, Cost-effectiveness of debrichem in managing hard-to-heal venous leg ulcers in the UK, *J of Wound Care* 31 (6) (June 2022).

- [2] M. Olsson, K. Jarbrink, U. Divakar, et al., The humanistic and economic burden of chronic wounds: a systematic review, *Wound Repair Regen.* 27 (1) (2019) 114–125, <https://doi.org/10.1111/wrr.12683>.
- [3] V.K. Shanmugam, K.S. Couch, S. McNish, R.L. Amdur, Relationship between opioid treatment and rate of healing in chronic wounds, *Wound Repair Regen.* 25 (1) (2017) 120–130, <https://doi.org/10.1111/wrr.12496>.
- [4] A. Cogo, C.A. Bignozzi, M.H.E. Hermans, B.J. Quint, J.P. Snels, G. Schultz, A desiccation compound as a biofilm- and necrosis-removing agent: a case series, *J. of Wound Care* 31 (10) (Oct.2022).
- [5] B. Wakefield, et al., A new option for chemical debridement using Debrichem to remove biofilm in hard-to-heal wounds. Published by MA Healthcare Ltd: St Jude's Church, Dulwich Road, London, *J of Wound Care* 32 (3) (2023) (Suppl 4), March.
- [6] G. Pini-Prato, C. Magnani, R. Rotundo, Nonsurgical treatment of peri-implantitis using the biofilm decontamination approach: a case report study, *Int. J. Periodontics Restorative Dent.* 36 (3) (2016) 383–391.
- [7] G. Pini-Prato, C. Magnani, R. Rotundo, Treatment of acute periodontal abscesses using the biofilm decontamination approach: a case report study, *Int. J. Periodontics Restorative Dent.* 36 (1) (2016) 55–63, <https://doi.org/10.11607/prd.2653>.
- [8] R. Wolcott, Providing a biofilm explanation for ablative treatment of recalcitrant wounds, *Today's Wound Clinic.* 10 (9) (2016) 12–18.
- [9] R.D. Wolcott, J.D. Hanson, E.J. Rees, et al., Analysis of the chronic wound microbiota of 2,963 patients by 16S rDNA pyrosequencing, *Wound Repair Regen.* 24 (1) (2016) 163–174, <https://doi.org/10.1111/wrr.12370>.
- [10] A. Goda, F. Maruyama, Y. Michi, I. Nakagawa, K. Harada, Analysis of the factors affecting the formation of the microbiome associated with chronic osteomyelitis of the jaw, *Clin. Microbiol. Infect.* 20 (5) (2014) O309–O317, <https://doi.org/10.1111/1469-0691.12400>.
- [11] P. Martini, C. Mazzatenta, G. Saponati, Efficacy and tolerability of fitostimoline in two different forms (soaked gauzes and cream) and citrizan gel in the topical treatment of second-degree superficial cutaneous burns, *Dermatol. Res. Pract.* 2011 (2011), 978291, <https://doi.org/10.1155/2011/978291>.
- [12] T. Bianchi, R.D. Wolcott, A. Peghetti, et al., Recommendations for the management of biofilm: a consensus document, *J. Wound Care* 25 (6) (2016) 305–317, <https://doi.org/10.12968/jowc.2016.25.6.305>.
- [13] D. Lauritano, M. Petrucci, G.M. Nardi, et al., Single application of a desiccating agent in the treatment of recurrent aphthous stomatitis, *J. Biol. Regul. Homeost. Agents* 29 (3 suppl 1) (2015) 59–66.
- [14] G. Lombardo, C. Signoretto, G. Corrocher, et al., A topical desiccant agent in association with ultrasonic debridement in the initial treatment of chronic periodontitis: a clinical and microbiological study, *New Microbiol.* 38 (3) (2015) 393–407.
- [15] R.A. Agha, T. Franchi, C. Sohrab, G. Mathew, et al., The SCARE 2020 guideline: updating consensus Surgical Case REport (SCARE) guidelines, *Int. J. Surg.* 84 (1) (2020) 226–230.
- [16] R. Fontaine, M. Kim, R. Kieny, Surgical treatment of peripheral circulation disorders [in German], *Helv Chir Acta.* 21 (5–6) (1954) 499–533.
- [17] Hermans MHE Combining an Acidic Compound and NPWT, Debridement and granulation in leg and foot ulcers, *Ann Case Report.* 7 (2022) 1101, <https://doi.org/10.29011/2574-7754.101101>.
- [18] Algharib A, Koning GG. Endovascular and conventional angioplasty, the challenges in modern patient-centered care. Editorial (Unpublished work: *Accepted for publication (In Press) Nov 2023 Science Progress Journal*).
- [19] J.T. Heikens, H.G. Gooszen, M.M. Rovers, et al., Stages and evaluation of surgical innovation: a clinical example of the ileo neorectal anastomosis after ulcerative colitis and familial adenomatous polyposis, *Surg. Innov.* 20 (5) (2013) 459–465, <https://doi.org/10.1177/1553350612468959>. Oct. (Epub 2012 Dec 14).
- [20] F. Keus, J. Wetterslev, C. Gluud, et al., Evidence at a glance: error matrix approach for overviewing available evidence, *BMC Med. Res. Methodol.* 1 (10) (2010) 90, <https://doi.org/10.1186/1471-2288-10-90>. Oct.
- [21] G.G. Koning, E.M. Adang, P.F. Stalmeier, F. Keus, P.W. Vriens, et al., TIPP and Lichtenstein modalities for inguinal hernia repair: a cost minimisation analysis alongside a randomised trial, *Eur. J. Health Econ.* 14 (6) (2013) 1027–1034, <https://doi.org/10.1007/s10198-012-0453-0>. Dec. Epub 2012 Dec 28. PMID: 23271350.
- [22] W.J.V. Bökkerink, G.G. Koning, P.W.H.E. Vriens, J. de Vries, Patients' perspective on inguinal hernia repair: a focus group study, *Asian J. Surg.* 44 (9) (2021) 1236–1237. Sep.