Medizinische Universität Graz

Final Report

Diagnostic Abilities of Ceramic Wound Dressings in Infected Wounds

Short title: DiACer

Principal Investigator:

Univ.Prof. Dr. Lars-Peter Kamolz MSc.
Department of Surgery
Division of Plastic, Aesthetic and Reconstructive Surgery
lars.kamolz@medunigraz.at
Tel: +43-316-385-14685

Co-Investigator:

Dr.med.univ. Hanna Luze
Department of Surgery
Division of Plastic, Aesthetic and Reconstructive Surgery
hanna.luze@medunigraz.at
Tel: +43-316-385-30445

Sponsor:

LIMBECK Medizinische Spezialartikel
Ganghofergasse 22, 1110 Vienna

Contact:
Richard Limbeck
richard.limbeck@limbeck.com

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1. Background

Wound infection of acute and chronic wounds is a major impairment in wound healing [1],[2]. For a diagnostic assessment, wounds are swabbed in order to develop a laboratory culture, which will establish the causative organism and ensure appropriate treatment. Only properly performed swab cultures provide useful data to augment diagnostic and therapeutic decision making. Despite the conventional use of swabs, a 'gold standard' method for wound sampling has not been confirmed yet [3].

Lately there is growing evidence on the use of the family of bacterial-binding dressings in the treatment of a variety of acute and chronic wounds [4]. The evidence in support of the bacterial-binding dressings is strongest in the area of infection prevention in surgical wounds. However, wound bioburden management in chronic wounds supported by a number of clinical studies as well.
A wide range of dressings including modern dressings with different kinds of biological activity are available [5]. Ceramic dressings such as Cerdak™ are used to absorb and retain large amounts of wound exudate containing (several) bacterial strains contaminating the wound bed. These dressings are regularly changed and disposed resulting in considerable amounts of medical waste with no further purpose. Instead of disposing these dressings after removal, a verification of bacterial strains could be investigated via sonication, maybe replacing conventional swabs in the future.
This pilot study aims to investigate diagnostic abilities of Cerdak™, a conventionally used ceramic dressing as a reliable method for the diagnosis of a chronic and acute wound infection.

2. Aim

The primary aim of this project was to investigate the potential of the ceramic dressing Cerdak™ in regard of absorbing infectious wound exudate and colony forming bacteria present in the wound moisture for a diagnostic purpose.
Via sonication of the removed dressings, different bacterial strains were detected and compared to those, detected via conventional swabs taken of the same wound.
The dressing changes and non-invasive analyzing methods were performed in 10 subjects presenting with clinically infected or contaminated wounds from different age groups (19-90 years). Detectable effects may establish a base for further clinical studies regarding diagnostic abilities of wound dressings and additional reliable methods for the diagnosis of a wound infection.

3. Study Design and Study Aims

3.1 Primary Aim

The primary aim of this study was the detection of bacterial strains colonizing the infected wound via sonication of Cerdak™ after the respective application time of approximately 2 days. Frequency of dressing changes were adapted to clinical findings. For clarity, an exemplary application time of 2 days

will be used in the following.

3.2 Secondary Aim

The secondary aim was to compare detectable bacterial strains to those, detected via conventional wound swabs. Comparison of the accuracy of both methods may reduce medical waste in the future, by using already required dressings for diagnostic purposes instead of additional wound swabs.

3.3 Primary Endpoint

The primary endpoint was the sonication of Cerdak™ after each terminated application time, e.g. after 2 and 4 days. Sonication revealed bacterial strains being present in infectious wound exudate and colonizing the wound.

3.4 Secondary Endpoint

The secondary endpoint was the comparison of detected bacterial strains via sonication and via conventional wound swabs. Furthermore, weight measurement of Cerdak™ has been performed before and after the application to determine absorption abilities.

4.4.1 Safety endpoints regarding the application area of Cerdak™ (at any time):

i. Increased redness
ii. Increased swelling
iii. Discomfort
iv. Itching
v. Subjects' wish to stop
vi. Any other adverse event listed under 12.0 within the study protocol

4. Study Population

4.1 Recruitment

Subjects elective for the study were recruited by the study team (staff of the Division of Plastic, Aesthetic and Reconstructive Surgery, Department of Surgery, Medical University of Graz). Subjects were informed about the study and its benefits for medical research by the study team. They have been handed an information sheet including all the details regarding the study and were asked to inform the staff about their decision on participating. Subjects were then screened for inclusion and exclusion criteria by the study team and signed the informed consent form. After obtaining the informed consent, the study personnel defined a subject ID, started with recording the subjects' demographics and wound characteristics (wound scoring). After completion, the study personnel performed a conventional wound swab, photo documentation, weight measurement and the first application of Cerdak™.

The sonication of Cerdak™ and following non-invasive analyzing methods (wound swabs, wound scoring, photo documentation) for the pilot study were approved by the Ethical Committee of the Medical University of Graz (EK 33-275 ex 20/21.)

4.2 Informed Consent

An informed consent, written in accordance with the origins of the Declaration of Helsinki and the applicable laws of Austria were obtained from all subjects before any trial related activities were started. The responsible physician explained the nature, purpose and risks of the study, provided the subject with a copy of the subject information sheet and asked for his written consent before she/he were included in the study.

4.3 Subject Inclusion Criteria

i. Male and female subjects, aged between 18-90 years willing to participate in this study

ii. Inpatient stay at the Department of Plastic, Aesthetic and Reconstructive Surgery, Medical University of Graz

iii. Presence of a conventionally treated wound showing clinical signs of infection, including:

- Local heat
- Redness/erythema
- Pain or tenderness
- Edema
- Inflammation
- Increased exudate
- Cellulitis
- Abscess/pus
- Purulent discharge
- Malodour
- Delayed healing
- Discoloration of wound bed
- Friable granulation tissue that bleeds easily
- Pocketing/ bridging at the base of the wound
- Wound breakdown

iv. Signed informed consent form

4.4 Subject Exclusion Criteria

v. Allergy to dressings (any kind)

vi. Known skin diseases or dermatoses (atopic dermatitis, psoriasis, etc.)

vii. Systemic infectious effects (sepsis, etc.)

viii. Current or planned pregnancy

ix. Unable to fully understand study procedures and to provide informed consent

5. Materials and Methods

5.1 Ceramic Dressing

The ceramic dressings used in this study are commercially available dressings (Cerdak™) produced by the company Cerdak LTD , Mtuzini, KwaZulu-Natal, South Africa and distributed via LIMBECK Medizinische Spezialartikel, Vienna, Austria. This ceramic dressings used in our study are CE certified (CE No.178B).
The standard Cerdak™ wound dressing consists of a sachet about the size of a teabag, filled with ceramic granules and sealed in a sterile pouch. The spherical micro-porous ceramic granules are loosely packed, allowing free access of air to the wound.
The most important properties of Cerdak™ wound dressing is micropore-driven capillary absorption, transport and storage of wound exudate and surface-area-driven adsorption of charged colloids suspended in wound liquids as well as odourous gases emanating from the wound. The mechanism of absorption, transport and storage of exudates is illustrated in *Fig.1*.

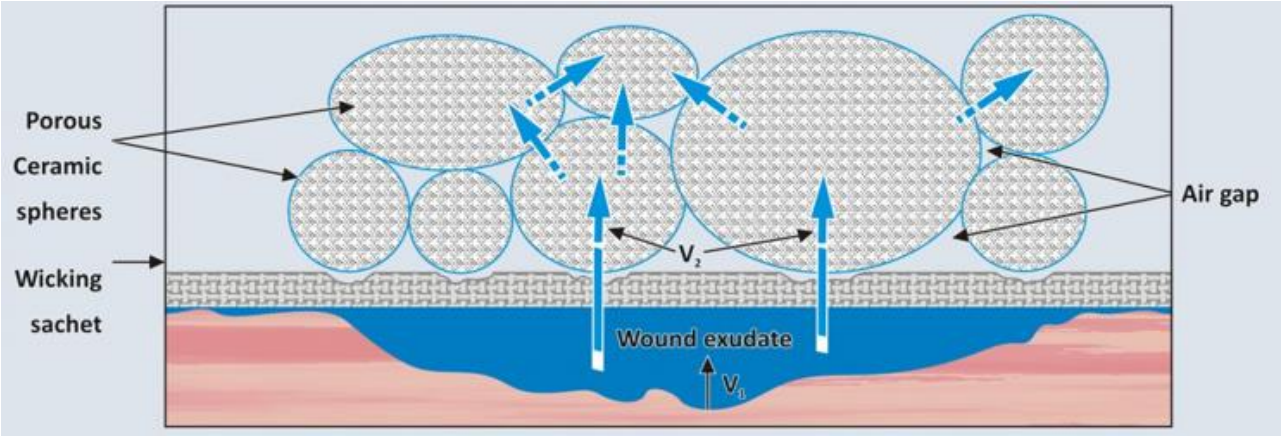


Figure 1: Mechanism of absorption, transport and storage of exudates by Cerdak™

The wound produces exudate at a rate V_1. This fluid passes through the wicking sachet and when it comes into contact with the ceramic with its high capillary suction force, it is absorbed at a rate V_2, which is much faster than the rate of supply. Since each ceramic granule is in point-contact with surrounding granules with similar high suction potential, moisture migrates continuously between the granules in an attempt to equalize the hydrostatic potential of all the granules in the sachet. There is however no driving force for the exudates to leave the ceramic granules, so that the interstitial air gaps between the granules remain dry and filled with air.

5.2 Wound Swabs

Conventional liquid based wound swabs (ESwab™, Copan Diagnostics Inc., California, USA) were taken before and after Cerdak™ application from the center to the outside of the wound using a zig-zag motion. After the procedure has successfully been completed, the sample and the pathological request form were labeled with the following:

- The patient's name, date of birth and identification number
- Site where the swab was taken
- Date and time of the sample
- Clinical indicators for taking the sample
- Any medication that may affect the results, i.e. antibiotics
- The clinical investigations required: microbiology, bacterial strains

5.3 Sonication

High power ultrasound at frequencies around 20kHz is capable of killing bacteria and for many years has been standard technique in microbiology for the disruption of living cells to release their contents. The use of low-intensity ultrasound for the disintegration of biofilm (sonication) on removed implants, dressings etc. and the subsequent culture of the sonication fluid is an alternative method to conventional tissue cultures for the diagnosis of bacterial strains.

Sonication of each Cerdak™ dressing was performed after removal. Dressings were placed in a sterile sonicate container and the request form was labeled with the above-mentioned parameters.

5.4 Wound scoring

Via wound scoring, wounds were characterized regarding size, infection parameters, necrosis etc. to assess wound healing and infection. Wound parameters of each subject will be recorded in a separate wound scoring sheet as presented in *Table 1*. The "Wound Score" is calculated of the following parameters: "Wound", "Granulation tissue", "Pus", "Crust", "Erythema", "Swelling" and "Necrosis".

Table 1: Wound Scoring

Study Visit	Wound	Size	Size	Granulation tissue	Pus	Crust	Erythema	Erythema Width	Erythema Width	Swelling	Necrosis
	Dry (0) Moist (1)	(mm)	(cm^2)	Full (0) Half (1) Empty (2)	Not present (0) Present (1)	Fallen off (0) Wound (1) Extended (2) None (3)	None (0) (1) (2) (3) Intense (4)	(mm)	<5mm (0) ≥5mm (1)	None (0) Medium (1) Intense (2)	None (0) Present (1) Extended 2-3mm (2) Extended >3mm (3) Eschar (4)
1											
2											
3											

5.5 Photo documentation

Photo documentation was performed before the dressing application and during the dressing changes to detect macroscopic changes. A tape measure to determine the size ratios was used in every picture. Study personnel ensured that the subjects' face was not visible.

6. Procedures

The collective of 10 subjects of the age of 18-90 years were included in this pilot project. After obtaining the informed consent, the study personnel defined a subject ID start with recording the subjects' demographics (Age, location of the wound), performed the wound scoring, photo documentation and a conventional wound swab as described under 5.2 to 5.5. The wound was cleaned with saline solution before the wound was debrided by the study personnel. Afterwards, Cerdak™ big enough to cover the entire wound was placed on the wound. The dressing was placed with the shiny (non-sticking) side of the sachet in direct contact with the wound bed. Dry gauze compresses and Cosmopor® E Dressings were placed on top to secure the primary dressing.

After the respective application time, e.g. two days, the first dressing change was scheduled. (Visit 2) After removal of Cerdak™, the dressing was packed for sonication. Furthermore, a conventional wound swab was taken, photo documentation and wound scoring was performed before a second Cerdak™ was placed in the center of the wound. After the same analyzing methods after the second application period, the study course was finished for the respective subject (Visit 5).
Figure 2 displays the experimental timeline of this pilot study.

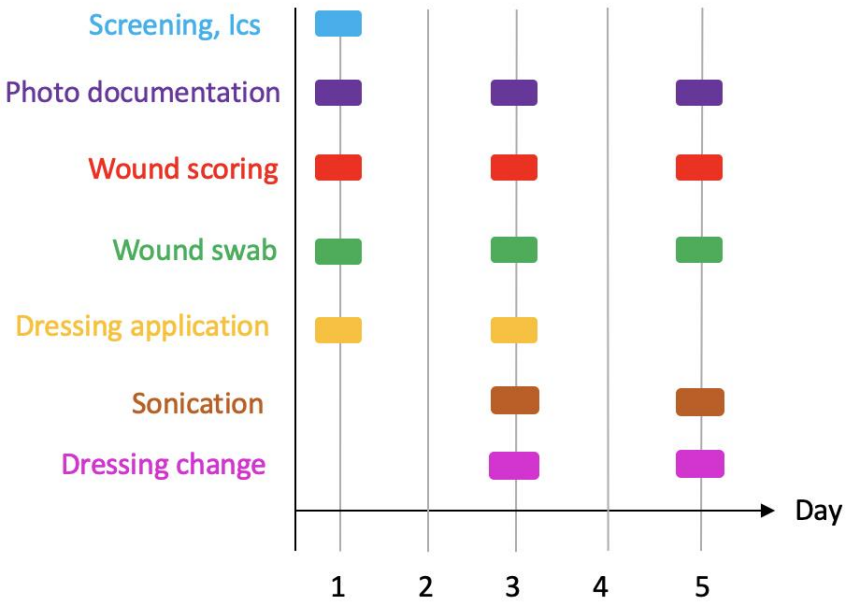


Figure 2: Experimental timeline. Frequency of dressing changes will be adapted to clinical signs. For overview clarity, an application time of 2 days is shown in this figure. Screening, ICs, wound scoring, wound swab and application of Cerdak™ on Day 1 during Visit 1. Dressings will be changed after e.g. 2 days (Visit 2), whereby Cerdak™ will be sent to microbiology sonication. The same analyzing methods will be performed before applying another Cerdak™ dressing. After the second cycle at Day 5 (Visit 3), all dressings will be removed. Photo documentation to detect macroscopic changes will be performed on the first, third and the last day of the study.

7. Statistics

7.1 Sample Size Calculation

This study is designed as a pilot study since no investigation of diagnostic abilities of ceramic dressings in infected wounds compared to conventional wound swabs has been performed yet. For this reason, no formal sample size calculation was performed. This pilot project ran in 10 patients aged 18-90.

7.2 Analysis of Data

Data has been documented on paper as well as in Microsoft Excel. The main analysis was based on an intention-to-treat (ITT) basis including all participants who completed at least one dressing change.

Normality testing was not performed given the small sample size and the expected low power thereof. Data is presented using means and standard deviation. Sensitivity of each detection method was calculated using cross-tabulation. Wound scoring and wound size were calculated using One-Way ANOVA with repeated measures and Friedman's test. The level of significance was set to $p < 0.05$. Prism 9.0.2 (GraphPad Software, LLC., San Diego, CA, USA) was used for statistical analysis.

8. Data Safety

No sensitive patient data will be disclosed to personnel of the present study. The information is restricted to age of the subject. Photographs of the application sites have been taken, never including the eyes of the patient. The patients were ascendingly assigned a study code (e.g. S01, S02,…, S10) Source document files will be kept throughout the whole study, documenting subjects data (study code, age and values calculated within non-invasive measurements (wound scoring)). All study related data is stored at the Medical University of Graz, Department for Surgery, Division of Plastic, Aesthetic and Reconstructive Surgery.

9. Results

A total of 10 subjects (9 male and 1 female) with an average age of 67.4 years (standard deviation (SD) of 11.0) were included in this study. A descriptive overview of the results is displayed in *Table 2*.
A total of 52 bacterial strains were detected via conventional swabs and sonication of Cerdak™ within the study course. 43 bacterial strains were detectable via sonication leading to a sensitivity of 82.7%. Out of these 43 detectable strains, 21 (48.8%) were not detected via conventional swabs.
31 bacterial strains were detected via conventional swabs leading to a sensitivity of 59.6%. 9 (29.0%) of 31 strains were not detected via sonication.

The mean wound size at Visit 1 was 62.58 cm^2 (SD 101.19 cm^2), at Visit 2 62.01 cm^2 (SD 101.35 cm^2) and at Visit 3 60.94 cm^2 (SD 101.67 cm^2). The difference in wound size showed no statistical significance (p= 0.20) over the study course.
The wound score at Visit 1 was in average 5.80 (SD 1.87), at Visit 2 6.00 (SD 2.11) and at Visit 3 5.90 (SD 2.33). The difference in wound score showed no statistical significance (p= 0.90) over the study course.

10. Conclusion

This project investigated the potential of the ceramic dressing CerdakTM in regard of absorbing infectious wound exudate and colony forming bacteria present in the wound moisture for a diagnostic purpose. Via sonication of the removed dressings, we were able to detect different bacterial strains with a sensitivity of 82.7%. In comparison, detection of bacterial strains via conventional swabs was possible with a sensitivity of 59.6%. In 9 (29.0%) of 31 strains detection via sonication was not possible.

This pilot project yields very promising results regarding diagnostic abilities of wound dressings and sonication of primary wound dressings as a new diagnostic approach, however to generate more significant results, we would suggest performing a broad-based and long-term study including a control group. Furthermore, detection of different biomarkers would be of utmost importance to add high diagnostic value. Detectable effects may establish a base for additional reliable methods for the exact diagnosis of a wound infection.

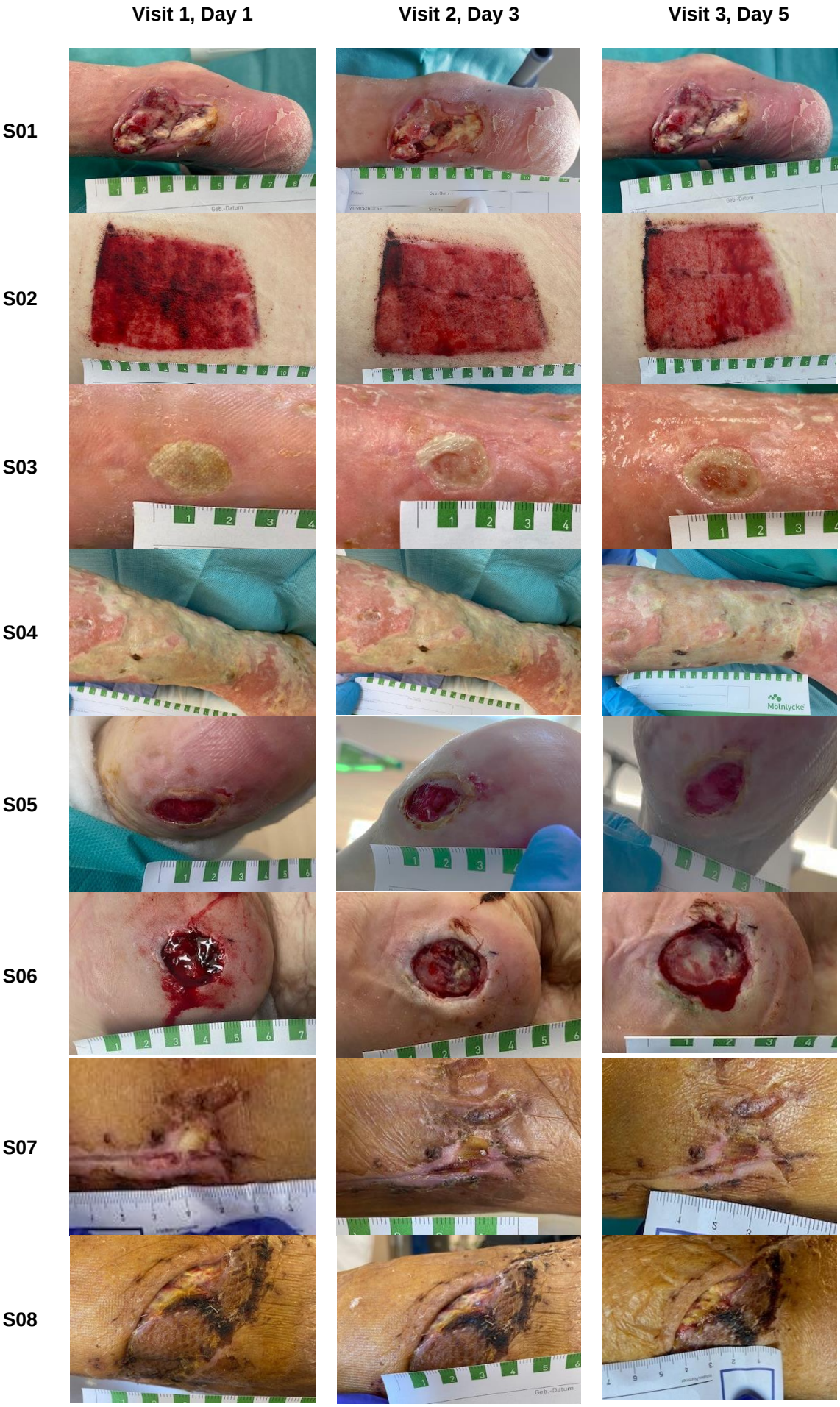
Table 2: Descriptive overview of the study population

Subject ID	Age [y]	Gender (m/f)	Wound Site	Antibiotics	No. of bact. strains Swab 1	Bact. strains Swab 1	No. of bact. strains Sonication 1	Bact. strains Sonication 1	No of bact. Strains Swab 2	Bact. strains Swab 2	No. of bact. strains Sonication 2	Bact. strains Sonication 2	No of bact. Strains Swab 3	Bact. strains Swab 3
S01	65	m	Lower leg right	NA	1	Staphylococcus aureus	1	Staphylococcus aureus	1	Staphylococcus aureus	1	Staphylococcus aureus	1	Staphylococcus aureus
S02	88	f	Upper leg left	NA	0	NA	1	Staphylococcus epidermidis	0	NA	0	NA	0	NA
S03	80	m	Lower leg right	NA	1	Alcaligenes faecalis	3	Alcaligenes faecalis, Corynebacterium striatum, Enterococcus faecalis	2	Alcaligenes faecalis, Corynebacterium striatum	2	Alcaligenes faecalis, Proteus mirabilis	1	Alcaligenes faecalis
S04	80	m	Lower leg left	NA	2	Proteus vulgaris, Pseudomonas aeruginosa	6	Proteus vulgaris,Enterobacter aerogenes, Enterobacter cloacae,Pseudomonas putida, Enterococcus faecium,Proteus mirabilis	4	Proteus mirabilis, Pseudomonas putida, Alcaligenes sp.,Enterococcus faecalis	5	Enterococcus faecalis,Proteus mirabilis,Enterococcus faecium,Pseudomonas putida, Enterobacter cloacae	3	Alcaligenes sp., Pseudomonas putida, Enterobacter cloacae
S05	61	m	Foot left	Dalacin 600mg	1	MRSA	2	MRSA, Proteus mirabilis	1	MRSA	1	MRSA	1	MRSA
S06	61	m	Sacrum right	Dalacin 600mg	2	MRSA, Corynebacterium aurimucosum	4	MRSA, Pseudomonas aeruginosa, Enterococcus faecalis, Proteus mirabilis	5	Proteus mirabilis, Citrobacter diversus, Pseudomonas aeruginosa, Enterococcus faecalis,Bacteroides fragilis	5	Citrobacter koseri,Staphylococcus caprae, Pseudomonas aeruginosa, Enterococcus faecalis, Proteus mirabilis	5	Pseudomonas aeruginosa, Proteus mirabilis,Enterococcus faecalis, Dermabacter hominis, Bacteroides fragilis
S07	62	m	Lower leg left	NA	1	Staphylococcus epidermidis	1	Staphylococcus epidermidis	1	Koagulase negative Staphylokokken	1	Staphylococcus epidermidis	0	NA
S08	62	m	Lower leg left	NA	0	NA	1	Enterococcus faecalis	0	NA	2	Proteus mirabilis, Enterococcus faecalis	0	NA
S09	56	m	Knee right	NA	0	NA	3	Bacillus cereus, Staphylococcus epidermidis, Staphylococcus haemolyticus	2	Staphylococcus epidermidis, Staphylococcus haemolyticus	2	Staphylococcus epidermidis, Staphylococcus haemolyticus	1	Staphylococcus epidermidis
S10	59	m	Lower abdomen right	NA	1	Staphylococcus haemolyticus	1	Proteus mirabilis	2	Pseudomonas aeruginosa, Proteus mirabilis	1	Proteus mirabilis	1	Pseudomonas aeruginosa

Abbreviations: Bacterial strains (Bact.strains); Female (f); Male (m); Not applicable (NA); Number (No.)

Table 3: Wound Scoring Day 1-5

	Subject ID	Wound	Size	Size	Granulation tissue	Pus	Crust	Erythema	Erythema Width	Erythema Width	Swelling	Necrosis	Wound Score
		Dry (0) Moist (1)	(mm)	(cm^2)	Full (0) Half (1) Empty (2)	Not present (0) Present (1)	Fallen off (0) Wound (1) Extended (2) None (3)	None (0) (1) (2) (3) Intense (4)	(mm)	<5mm (0) ≥5mm (1)	None (0) Medium (1) Intense (2)	None (0) Present (1) Extended 2-3mm (2) Extended >3mm (3) Eschar (4)	
Visit 1 Day 1	S01	1	60x40	24	0	0	1	1	5	0	0	3	6
	S02	1	90x50	45	2	0	1	1	10	1	0	0	6
	S03	1	15x20	3	0	0	1	0	0	0	1	1	4
	S04	1	200x160	320	0	1	1	1	5	0	1	2	7
	S05	1	25x15	3.75	0	0	1	1	5	0	0	0	3
	S06	1	20x20	4	0	0	1	0	0	0	1	0	3
	S07	1	20x10	2	2	0	1	1	6	1	1	1	8
	S08	1	40x20	8	0	0	2	1	6	1	2	1	8
	S09	1	60x45	27	1	0	1	1	5	1	0	1	6
	S10	1	270x70	189	1	0	3	0	0	0	1	1	7
Visit 2 Day 3	S01	1	60x40	24	0	0	1	1	5	1	1	3	8
	S02	1	90x45	40,5	2	0	1	1	7	1	0	0	6
	S03	1	13x20	2,6	0	0	1	0	0	0	1	1	4
	S04	1	200x160	320	0	1	1	1	5	0	1	3	8
	S05	1	25x15	3,75	0	0	1	1	4	0	0	0	3
	S06	1	20x20	4	0	0	1	0	0	0	1	0	3
	S07	1	20x10	2	2	0	1	1	5	1	1	1	8
	S08	1	40x18	7,2	0	0	2	1	6	1	2	1	8
	S09	1	60x45	27	1	0	1	1	4	0	0	1	5
	S10	1	270x70	189	1	0	3	0	0	0	1	1	7
Visit 3 Day 5	S01	1	60x40	24	0	0	1	1	3	0	1	3	7
	S02	1	85x40	34	2	0	1	1	6	1	0	0	6
	S03	1	13x20	2,6	0	0	1	0	0	0	1	1	4
	S04	1	200x160	320	0	1	1	1	5	0	1	3	8
	S05	1	25x15	3,75	0	0	1	1	4	0	0	0	3
	S06	1	20x20	4	0	0	0	0	0	0	1	0	2
	S07	1	20x10	2	2	0	1	1	4	1	1	1	8
	S08	1	40x15	6	2	0	2	1	4	0	2	1	9
	S09	1	60x40	24	1	0	1	1	4	0	0	1	5
	S10	1	270x70	189	1	0	3	0	0	0	1	1	7


Visit 1, Day 1
Visit 2, Day 3
Visit 3, Day 5
S01
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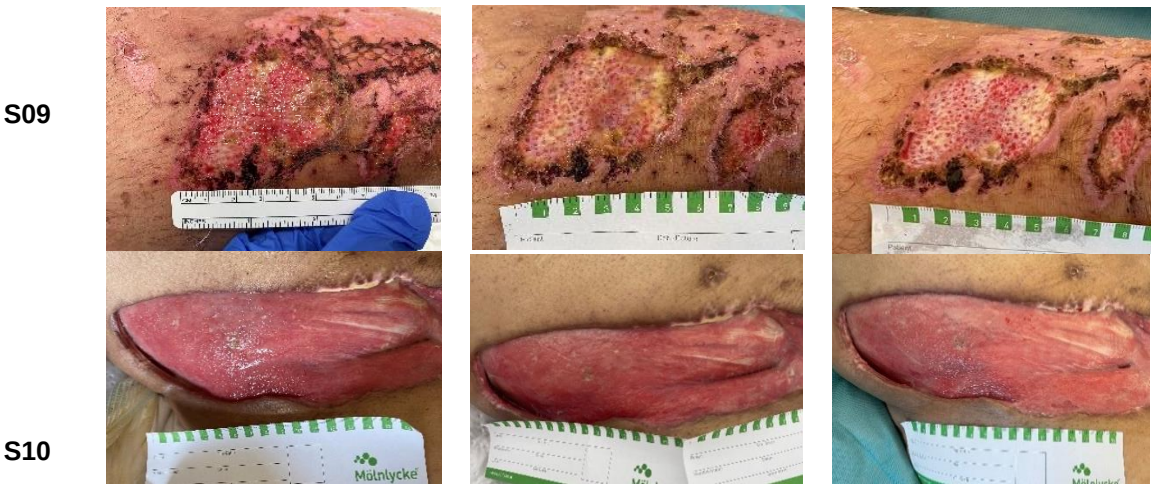

Figure 3: Photo documentation of each subject within the study course.

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