

Qualitative Bacteriology in Malignant Wounds— A Prospective, Randomized, Clinical Study to Compare the Effect of Honey and Silver Dressings

Betina Lund-Nielsen, MHS; Lis Adamsen, PhD; Finn Gottrup, MD; Mikael Rorth, MD; Anders Tolver, PhD; and Hans Jorn Kolmos, MD

Abstract

Between 5% and 10% of cancer patients develop malignant wounds. *In vitro* and some clinical studies suggest that silver- or honey-coated dressings may have an antibacterial effect in nonmalignant wounds, but their possible antibacterial effect in malignant wounds remains unknown. A prospective, randomized, single-blind controlled clinical study was conducted to evaluate the bacteriology of malignant wounds and compare the effect of a honey-coated (Group A) to a silver-coated (Group B) dressing on the qualitative bacteriology of malignant wounds. All wound interventions were performed by the same healthcare professional. Swab cultures were obtained at baseline and following a 4-week intervention and were evaluated without information about the patient treatment group. Of the 75 patients with advanced cancer and malignant wounds identified, 67 (34 in group A, 33 in group B; median age 64 years, range 47–92) consented to participate and completed the 4-week study. The majority were women (88%) with breast cancer (79%). No statistically significant differences were found between the type and number of different wound pathogens in the wounds during the course of the study or between Group A and Group B. Neither anti-neoplastic nor antibiotic treatment influenced the presence of wound pathogens. *Staphylococci* were found in 42%, enteric bacteria in 34%, anaerobic bacteria in 16%, *Pseudomonas* in 10%, and hemolytic streptococci in 6% of wounds at baseline; in total, 25 different bacterial species were identified. Sixty-one percent (61%) of wounds decreased in size following treatment, but no significant differences were observed between the type and variety of wound pathogens and whether wound size decreased. Although quantitative bacteriological changes may have occurred, the possible antibacterial effect of the honey or silver dressing could not be confirmed in these malignant wounds. Routine wound swabbing of malignant wounds is of little value and should be restricted to cases where signs of infection requiring antibiotic intervention are observed or where resistant organisms require special infection control measures.

Key Words: randomized controlled study, malignant wound, cultures, honey-coated dressing, silver-coated dressing

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An estimated 5% to 10% of all cancer patients develop malignant wounds.¹ The wounds that often occur in advanced stage cancer result from tumors that infiltrate the skin and underlying tissues.² The base of the malignant wound is characterized by the presence of necrotic and tumor tissue, slough, and fibrin, stimulating the growth of anaerobic bacteria that can produce odor and infection in the wound.^{3,4} Complete healing, as a rule, is not a realistic outcome in this

type of patient due to the presence of cancer tissue in the wound base.⁵

One could speculate that if dressings with antibacterial properties could reduce the growth of bacteria and resultant odor in the malignant wound, optimal healing could be facilitated. Both honey^{6,7} and silver dressings⁸ have shown antibacterial effects in other chronic wounds such as leg ulcers, but there is no evidence from randomized clinical trials (RCTs)⁹

Ms. Lund-Nielsen is a research nurse and Dr. Adamsen is a Professor, The University Hospitals Centre for Nursing and Care Research (UCSF), Copenhagen University Hospital, Copenhagen, Denmark. Dr. Gottrup is a Professor, Copenhagen Wound Healing Center, Bispebjerg Hospital. Dr. Rorth is a Professor, Department of Oncology, Rigshospitalet, University Hospital of Copenhagen. Dr. Toliver is an Associate Professor, Department of Basic Sciences and Environment, Faculty of Life Sciences, Copenhagen, Denmark. Dr. Kolmos is Professor, Department of Clinical Microbiology, Odense University Hospital, Denmark. Please address correspondence to: Betina Lund-Nielsen, The University Hospitals Centre for Nursing and Care Research (UCSF), Department 7331, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark; email: Betina.Lund-Nielsen@rh.regionh.dk.

about their effect on malignant wounds, and no controlled studies exist that compare the effect of silver-coated versus honey-coated dressings in chronic wounds.

The aim of this study is to compare the effect of honey-coated and silver-coated dressings on the qualitative bacteriology in malignant wounds.

Materials and Methods

Design. The investigation was part of a larger study (Lund-Nielsen et al. In press) designed to compare two dressing regimens over a 4-week intervention period in cancer patients with advanced disease and malignant wounds (n = 75). The Group A regimen consisted of a honey-coated primary dressing (Algivon/Activon Tulle UMF 12+ [AdvaNordic Medical Group A/S]) covered with an absorbent dressing (Sorbion/Drymax [Mediq Danmark A/S]) and foam dressings (Allevyn Adhesive [Smith & Nephew A/S]). The Group B regimen consisted of a silver-coated primary dressing (Acticoat/Acticoat Absorbent [Smith&Nephew A/S]) and a secondary foam dressing (Allevyn Adhesive [Smith&Nephew A/S]). Both treatment groups also received psychosocial support and relaxation training. The project was designed as a prospective, randomized clinical intervention study as well as an exploratory, qualitative, interview study (registered under the identification number NCT00435474 at www.clinicaltrials.gov). Approval was received from the Danish National Data Inspectorate (2006110013A). The study adheres to guidelines set by the Ethical Research Committee for Copenhagen and Frederiksberg municipalities ([KF] 01 2006-5491).

The primary goal was to investigate the extent to which honey-coated dressings, compared with silver-coated dressings, could reduce wound size. A secondary goal was to investigate whether the two types of dressings influenced the presence of potential wound pathogens that may increase the risk of wound infection in the malignant wound.

Participants. Seventy-five (75) consecutive patients with advanced stage cancer and malignant wounds were identified and recruited from oncology units in 10 hospitals in Denmark. Whether a wound could be characterized as a malignant wound was established through clinical signs, not through biopsies. The clinical diagnosis was presented as a nonhealing wound that developed through the growth of a tumor through the skin or occurred in connection with metastases.

Key Points

- The purpose of this randomized, controlled clinical study was to compare the effect of honey-coated and silver-coated dressings on the qualitative bacteriology in malignant wounds in 67 patients.
- Almost all wounds contained at least one type of pathogen, and the qualitative bacteriological results did not differ over time or between the two types of dressings used.
- The authors conclude that swab cultures of malignant wounds should not be routinely performed and that the potential antibacterial effect of the dressings used could not be confirmed in this patient population.

Danish-speaking cancer patients were included in the study if they met the following criteria: 18 years of age or older, had malignant wounds and advanced stage cancer (metastases to the lungs, bones, liver, or cancer outside of the localized region of the tumor), a survival prognosis of >3 months, and had not received radiation therapy to the wound area for the past 3 months. Patients undergoing anti-neoplastic treatment (eg, chemotherapy, anti-hormone treatment) and/or systemic antibiotic treatment were included.

Three of the 75 patients identified did not want to participate in the study or wish to use a dressing. Baseline and

Table 1. Demographic and medical characteristics of study participants

	Group A: Manuka honey (n=34)	Group B: Silver dressing (n=33)	Total	P value
Age (year)				
Median	65	60	64	0.470
Range	5-86	47-90	47-90	
Gender				1.000
Female	30	29	59 (88%)	
Male	4	4	8 (12%)	
Cancer diagnosis				0.618
Breast	27	26	53 (79%)	
Head/neck	5	3	8 (12%)	
Others	2	4	6 (9%)	
Anti-neoplasm treatment				0.765
Yes	28	26	54 (81%)	
No	6	7	13 (19%)	
Antibiotic treatment				0.341
Yes	4	7	11 (16%)	
No	30	26	56 (84%)	
Wound duration (months)				0.980
Median	7.5	6.5	7	
Range	1-86	1-48	1-86	

Table 2. Number of wound pathogen isolates at baseline and after 4 weeks

Groups of wound pathogens	Bacteria species	Number of wounds containing isolate			
		Group A: Manuka honey dressing n=34		Group B: Silver dressing n=33	
		Baseline	4 weeks	Baseline	4 weeks
Anaerobic bacteria	<i>Bacteroides fragilis</i>	1	1	0	0
	<i>Bacteroides</i> species	1	1	3	1
	<i>Porphyromonas</i> species	1	1	2	1
	<i>Prevotella</i> species	1	0	1	2
	<i>Peptococcus</i> species	1	0	0	1
	<i>Peptostreptococcus</i> species	0	1	0	0
Enteric bacteria	<i>Escherichia coli</i>	4	3	2	1
	<i>Enterobacter cloacae</i>	5	3	2	2
	<i>Klebsiella oxytoca</i>	0	1	2	2
	<i>Klebsiella pneumoniae</i>	1	3	0	0
	<i>Morganella morganii</i>	0	0	1	0
	<i>Proteus mirabilis</i>	0	1	0	1
	<i>Proteus vulgaris</i>	0	1	2	0
	<i>Enterococcus faecalis</i>	2	6	4	3
	<i>Enterococcus faecium</i>	1	0	0	0
Pseudomonads	<i>Pseudomonas aeruginosa</i>	3	3	4	2
	<i>Pseudomonas</i> species	1	0	2	2
	<i>Pseudomonas stutzeri</i>	0	0	1	0
	<i>Stenotrophomonas maltophilia</i>	1	1	3	2
Hemolytic Streptococci	Hemolytic Streptococci group B	1	5	1	4
	Hemolytic Streptococci group C	0	0	1	1
	Hemolytic Streptococci group G	1	1	0	1
Staphylococci	<i>Staphylococcus aureus</i>	15	16	13	14
	<i>Staphylococcus lugdunensis</i>	0	0	1	0
Other pathogens	<i>Pasteurella canis</i>	0	0	0	1

follow-up data from another five patients was not available, three patients died during the intervention period, and the wounds of two patients healed during the intervention, leaving a sample of 67 cancer patients (see Table 1).

When participants had given consent, they were randomized to Group A (honey-coated dressing) or Group B (silver-coated dressing). The Clinical Research Unit (KFE) at Department of Oncology, Copenhagen University Hospital — Rigshospitalet administered the computer-based randomization process. Stratification was used for gender, cancer diagnosis (+/- breast cancer), and treatment (+/- anti-neoplastic treatment).

Intervention. Wound care was administered in the patient's home every 2 to 3 days. Each visit lasted approximately 90 minutes. The first author, together with the patient and/or the wound care nurse, administered the wound care: cleansing with tap water and liquid medicinal soap (pH factor 4.5), and continued with the aid of tweezers and nonwoven pads. Modern wound healing principles were used, including cleansing routines and moist wound healing with application of either honey or silver dressings in combination with foam dressings.

Clinical and bacteriological procedures. Qualitative wound swabbing was performed at baseline and after completing the 4-week intervention. Digital photographs were taken that showed the precise measurements of the wound in mm² using the software Quantify Image Central® (K:L:O:N:K. Denmark).¹⁰

Wounds were swabbed using a charcoal swab stick. The lab investigation was solely qualitative—ie, it involved registering the presence of the different species of wound pathogens irrespective of their concentration. First, the wound was cleansed, after which a charcoal swab stick was rotated 360° over the surface of the wound and in a representative area measuring 1 cm x 2 cm. The swabbed area then was documented so swabbing following the intervention would involve the same wound area as before the intervention. Once swabbing was completed, the swab stick was placed in Stuart's transport medium and sent directly to the laboratory, where the specimens were cultured on aerobic 5% blood agar plates, blue plates (modified Conradi-Drigalski), and anaerobic plates (chocolate agar with vitamin K and cystein). The blood plates then were incubated in 5% CO₂, blue plates in atmospheric air at 35° C, and anaerobic plates in an anaerobic cabinet at 37° C.

Table 3. Number of wounds containing isolates by major group and concomitant treatment

Groups of wound pathogens	Treatment		Antibiotic		Anti-neoplasm	
	Honey (n=34)	Silver (n=33)	Yes (n=11)	No (n=56)	Yes (n=54)	No (n=13)
Anaerobic bacteria						
Baseline	5	6	1	10	9	2
After 4 weeks	4	5	0	9	8	1
Enteric bacteria						
Baseline	11	12	6	17	19	4
After 4 weeks	15	9	6	18	19	5
Hemolytic <i>Streptococci</i>						
Baseline	2	2	0	4	1	3
After 4 weeks	6	6	1	11	7	5
<i>Pseudomonas</i>						
Baseline	3	4	1	6	5	2
After 4 weeks	3	2	1	4	4	1
<i>Staphylococci</i>						
Baseline	15	13	4	24	21	7
After 4 weeks	16	14	3	27	23	7

Table 4. Distribution of patients by number of wound pathogens and treatment at baseline and after 4 weeks

Number of wound pathogens	Baseline		Week 4	
	Honey (n=34)	Silver (n=33)	Honey (n=34)	Silver (n=33)
0	2	0	2	3
1	16	13	12	15
2	10	15	10	13
3	3	3	7	1
4	3	2	3	1

Readings for the bacteria were performed 2 days following lab procedures. The primary purpose of the lab findings was to ascertain the presence of hemolytic *Streptococci*, *Staphylococci*, *Pseudomonas*, enteric bacteria, and anaerobic bacteria, and whether any of them were multidrug resistant—eg, methicillin-resistant *Staphylococcus aureus* (MRSA) (see Table 2). Identification and susceptibility testing were performed by routine methods used by the laboratory. All laboratory analyses were performed without indication of patient treatment group.

Primary data analysis and statistics. A power calculation in a two-sided significance test showed that 70 patients should be included in order to prove a 20% difference between the two treatments for the primary study purpose concerning

wound size. Mann-Whitney U tests and Fisher's exact tests were used to compare the baseline characteristics of the treatment groups before the intervention. Binary outcomes measuring the prevalence of various bacterial groups were analyzed using a logistic regression model with treatment group and time (before/after completing of the intervention) as explanatory variables. A treatment effect during the intervention period corresponded to an interaction between treatment and time. Test for changes in the prevalence of a bacterial group corresponded with a main effect of time. A procedure for logistic regression was used, taking into account the within-subject correlation among samples from the same patient¹¹ as well as a Stuart-Maxwell test for marginal homogeneity to test for changes in the matched-pairs data recording the number of bacterial species present in each wound before and after intervention.¹² Finally, Fisher's exact test was used to explore if wound microbiology post-intervention depended on whether wound size decreased during the intervention

period. All *P* values were evaluated at a 5% significance level after a Bonferroni correction for multiple testing. The statistical analyses were made using *R: A Language and Environment for Statistical Computing*, version 2.10.1.¹³

Results

The median age of the 67 patients was 64 years (range: 47–90 years). The majority of participants (88%) were women, 79% had breast cancer, 81% were undergoing anti-neoplastic treatment with chemotherapy or anti-hormone treatment, and 16% were undergoing systemic antibiotic treatment. The median wound duration before intervention was 7 months (range 1–86). Baseline characteristics were similar in both groups.

No wound pathogens were found at the intervention baseline in two malignant wounds. The remainder showed colonization with one to four different wound pathogens (median = 2). At baseline, 25 different species in total were detected (see Table 2); *S. aureus* was the most prevalent species (found in 42% of wounds). None of the isolates was MRSA. Enteric bacteria were cultured in 34%, *Pseudomonas* in 10%, and hemolytic streptococci was detected in 16% at baseline. In 69% of wounds, the same species were found before and after the intervention.

The distribution of wound pathogens was the same in both wound dressing groups, both at baseline and after 4 weeks (see Table 3). Similarly, the distribution of pathogens did not differ between patients who did and did not receive antibiotic (eg, metronidazol, doxycycline) or anti-neoplastic treatment (eg, chemotherapy, anti-hormone-treatment).

Table 5. Distribution of wound pathogen presence by treatment and wound size reduction after 4 weeks

Wound pathogen present at week 4	Group A: Manuka honey Wound size reduction		Group B: Silver dressings Wound size reduction	
	Yes	No	Yes	No
	(n=23)	(n=11)	(n=18)	(n=15)
Anaerobic bacteria	4 (17%)	0 (0%)	2 (11%)	3 (20%)
Enteric bacteria	11 (48%)	4 (36%)	5 (28%)	4 (27%)
Hemolytic <i>Streptococci</i>	5 (22%)	1 (9%)	2 (11%)	4 (27%)
<i>Pseudomonas</i>	1 (4%)	3 (27%)	0 (0%)*	5 (33%)*
<i>Staphylococci</i>	12 (52%)	4 (36%)	6 (33%)	8 (53%)

* $P = 0.013$ for comparing the prevalence of *Pseudomonas* in Group B

Table 6. Distribution of patients by number of wound pathogens, treatment group, and wound size reduction after 4 weeks

Number of wound pathogens	Group A: Manuka honey Wound size reduction		Group B: Silver dressing Wound size reduction	
	Yes	No	Yes	No
	(n=23)	(n=11)	(n=18)	(n=15)
0	2	0	3	0
1	7	5	10	5
2	5	5	5	8
3	6	1	0	1
4	3	0	0	1

At baseline, no significant difference was found between the two treatment groups in number of species ($P = 0.54$) (see Table 4). Only two patients had no wound pathogens at baseline. The majority of patients (54) had one or two wound pathogens. Overall, a Stuart-Maxwell test for marginal homogeneity between the matched number of species before and after intervention for individual patients revealed no significant change for either of the treatment groups (honey: $P = 0.60$, silver: $P = 0.26$).

Median change of wound size was -15 cm^2 (range -221 to 160) for the honey group and -3 cm^2 (range -67 to 679) for the silver group. Wound size reduction was documented for 23 (67%) wounds in the honey and 18 (54%) wounds in the silver dressing group (see Table 5).

No significant differences between wounds that did or did not reduce in size and the prevalence of a particular group of wound pathogens after the 4-week intervention could be demonstrated. *Pseudomonas* had a tendency to be found less often in wounds that decreased in size ($P = 0.089$ and $P = 0.013$ for honey and silver dressings, respectively).

The presence or absence of decreased wound size after 4 weeks also did not significantly affect wounds with zero, one, two, three, or four different bacterial species (see Table 6) in

either the honey ($P = 0.318$) or silver ($P = 0.084$) dressing group.

Discussion

To the authors' knowledge, the current investigation is the first randomized study that compares the effect of honey-coated versus silver-coated dressings on bacteriology in malignant wounds in patients with advanced-stage cancer. No statistically significant difference was found in wound pathogen distributions over time or between the honey and silver dressing group. Neither anti-neoplastic nor antibiotic treatment influenced the occurrence of wound pathogens. No significant association between a reduction in wound size and prevalence of a particular group of wound pathogens after intervention could be demonstrated.

The wounds showed colonization with one to four different wound pathogens (median = 2). *Staphylococci* were found in 42%, enteric bacteria in 34%, and *Pseudomonas* in 10% of wounds. In total, 25 different species were identified.

A clinical study¹⁴ that included seven patients with venous ulcers found that silver-released dressings contributed to wound bed preparation, but did not attain a germ-free status. In their review, Fong and Wood¹⁵ indicated that nanocrystalline silver dressing is an effective antimicrobial for treating chronic wounds. In his review of 17 RCTs involving 1,965 patients treated with honey and 16 trials involving 533 wounds on experimental animals, Molan¹⁶ showed that honey's antibacterial activity clears infection and protects wounds from becoming infected. However, in the current study, researchers did not observe an effect of these dressings on wound microbiology in malignant wounds. Contrary to other chronic wounds, malignant wounds are under the continuous influence of the cancer's general progressive character and possible effects of the systemic treatment. This can lead to continuous tissue deterioration with a large volume of necrosis and slough. In the current study, culture results suggest that anti-neoplastic treatment with, for example, chemotherapy and anti-hormone treatment may not change these circumstances. As such, the wound pathogens have optimal growth conditions, and a continuous colonization of malignant wounds should be expected. This is also reflected in the results—97% of the wounds in the present study were colonized with between one and four species of wound pathogens (median = 2).

Mainly *in vitro* studies¹⁷⁻²⁰ have demonstrated that honey-coated and silver-coated dressings have an antibacterial effect against *Staphylococci*, enteric bacteria, and *Pseudomonas*. An RCT by Gethins²¹ ($n = 108$) that compared the effect of

honey-coated dressings and hydrogel on bacteriology in chronic leg ulcers showed that Manuka honey was effective in eliminating MRSA from 70% of 16 leg ulcers infected with MRSA, and that *S. aureus* was the most common species present (38%). In a clinical study of 86 patients with traumatic and nonhealing wounds, Ziegler et al²² found that silver had antimicrobial activity against *Staphylococci*, MRSA, *Pseudomonas*, and *Klebsiella pneumoniae*.

The current study found no statistically significant difference in bacteriology between the two treatment groups, nor was a difference detected in the number and variety of species when comparing baseline to 4-week intervention culture results. *S. aureus* was the most prevalent species (found in 42% of wounds). No MRSA was detected, probably a reflection of its low presence in the authors' country.²³

Antibiotic treatment had no influence on the prevalence of the five groups of wound pathogens; in 69% of the wounds, the same species were found before and after the intervention period. Optimal effect of systematic antibiotic treatment requires vital and well-vascularized tissue. Most likely, the burden of tumor in the wound compromises vascularization, thereby reducing the effect of antibiotics.

Some of the authors' cancer patients receive antibiotics (eg, metronidazol, doxycycline) regularly in order to diminish the odor from the wound. Other of their patients receive antibiotics based on positive swab results, with no obvious signs of clinical infection (increase in temperature, redness and swelling of the tissue, pain, increased exudation). In the current study, 97% of the wounds were colonized with at least one type of wound pathogen. Extrapolating from that finding, swabbing from the malignant wound will in most cases show a series of wound pathogens that do not necessarily affect the wound or the patient's condition. Therefore, taking qualitative swabs from malignant wounds is not indicated unless clinical signs of infection are present or if MRSA is suspected. Further, current study results suggest that antibiotic treatment has little impact on the presence of bacteria in the malignant wounds and that assessing bacterial flora is not a suitable means of monitoring the clinical effect of treatment. Although the purpose of this study was not to evaluate healing outcomes, it is important to note that, with the possible exception of *Pseudomonas*, the proportion of wounds that did or did not exhibit a reduction in wound size did not appear to be effected by the number and type of bacteria present at the end of the intervention period.

Study strengths include randomization, single-blind (laboratory) analysis, and participation of a national cohort of patients from all oncology units in Denmark and representative of patients with malignant wounds. In addition, the same person performed the swabbing using established guidelines before and after completing the intervention throughout the entire data collection period, eliminating variegation in methods. The same type and brand wound care products were used throughout the entire study period, and procedures were performed in the same way by the first author and the trained wound care nurses she supervised.

Limitations

Limitations of the study include its small size and the fact that there was no untreated control group. The authors' pilot study² (n = 12) investigated the effect of silver-coated dressings versus no treatment in breast cancer wounds. Nine cancer wounds (75%) showed improvement using silver-coated dressings. Because post-intervention results were promising, including an untreated control arm in subsequent studies was considered unethical. Similarly, although regular routine swabbing techniques provide qualitative data only, a quantitative culture technique that would have provided more details was considered too invasive for this group of patients.

In a practice guideline, Dow²⁴ describes swab cultures as able to reliably detect bacteria in chronic wounds. Pellizzer et al,²⁵ comparing deep tissue biopsy to superficial swab culture monitoring techniques to assess diabetic foot infections, noted no statistical differences between the two procedures in detecting bacteria. In that study, the mean number of isolates per patient was 2.34 using swabbing and 2.07 by tissue biopsy. As such, swabs provided a reliable assessment of wound pathogens present, which can be interpreted as a relevant measure of the effect of the intervention. The method was advantageous in that it complies with the routine used in most microbiological laboratories, and as such the results directly correlate with clinical practice.

Conclusion

Malignant wounds are chronic wounds in which the progressive nature of cancer causes the production of tumor tissue, necrosis, and slough in the wound that triggers chronic colonization with wound pathogens. In this study, honey-coated or silver-coated dressings had no effect on the qualitative bacteriology of malignant wounds, and use of antibiotic or anti-neoplastic treatment did not affect culture results. Culture results also did not differ between wounds that did or did not reduce in wound size, suggesting that routine qualitative wound swabbing of malignant wounds is of little value. Swabbing malignant wounds may be restricted to cases with signs of infection requiring intervention with antibiotics or when the presence of MRSA or other antimicrobial-resistant organisms is suspected, and special infection control restrictions may be needed. ■

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