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Maggot Therapy for Wound Debridement

A Randomized Multicenter Trial

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Objective: To study the efficacy of bagged larvae on wound debridement compared with conventional treatment.

Design: Randomized, multicenter, controlled, prospective phase 3 trial with blinded assessment of outcome measures by a single observer.

Setting: Two hospital referral centers in Caen and Lyon, France.

Patients: Random sampling of 119 patients with a non-healing, sloughy wound 40 cm² or smaller, less than 2 cm deep, and an ankle brachial index of 0.8 or higher.

Intervention: During a 2-week hospital stay, patients received either maggot debridement therapy (MDT) or conventional treatment. At discharge, conventional dressings were applied and a follow-up visit occurred at day 30.

Main Outcome Measure: Percentage of slough in wounds at day 15.

Results: There was a significant difference between groups at day 8 (54.5% in the MDT group and 66.5% in the control group) ($P=.04$). The mean percentage of slough at day 15 was 55.4% in the MDT group and 53.8% in the control group ($P=.78$).

Conclusions: Although MDT shows no significant benefit at day 15 compared with conventional treatment, debridement by MDT is significantly faster and occurs during the first week of treatment. Because there is no benefit in continuing the treatment after 1 week, another type of dressing should be used after 2 or 3 applications of MDT.

Trial Registration: clinicaltrials.gov Identifier: NCT01211236

Arch Dermatol.

Published online December 19, 2011.

doi:10.1001/archdermatol.2011.1895

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WOUND-BED PREPARATION with wound debridement not only helps to remove damaged tissue and biofilms and restore normal bacterial flora, it also improves growth factors and senescent cell activities.^{1,2} In addition, debridement helps to repair the defective remodeling of extracellular matrix proteins and prevent the failure of reepithelialization.³⁻⁵ The effects of maggots on wounds have been divided into 3 general mechanisms: debridement, antibacterial effects, and stimulation of wound healing.⁶⁻¹² In 2004, the US Food and Drug Administration approved medical maggots as a device prescribed by physicians. Relatively few clinical studies¹³⁻¹⁵ have been conducted and the results are not clear, partly owing to methodologic assessment problems.

A randomized, controlled, prospective phase 3 clinical trial to study the ef-

ficacy of bagged larvae on wound debridement in comparison with conventional treatment was performed. The primary objective was to compare the mean percentage of slough in wounds treated with maggot debridement therapy (MDT) with that of conventional treatment at day 15. Secondary objectives were to assess debridement (at days 8 and 30), wound healing (at days 8, 15, and 30), treatment-related pain, microbiologic modification in the presence of gram-positive and gram-negative bacteria, adverse events, comfort of the dressing, and time spent for wound care.

METHODS

From March 1, 2005, to December 31, 2008, a randomized study was conducted in 2 hospital referral centers in Caen and Lyon, France. It was approved by the ethics committee of the Université de Caen (CPP 2005-05). All participants signed an informed consent form.



Figure 1. The enclosed dressing (Vitapad; BioMonde Laboratories) used in the trial. Eighty sterile maggots are inserted into each dressing (the device is shown without maggots here to display the inner layers).

PATIENTS

Patients with a nonhealing, sloughing wound of 40 cm² or less on the lower limb were included in the study. The limb wounds were venous ulcers with an ankle brachial index of 0.8 or higher. Exclusion criteria were pregnancy or lactation, neuropathy and/or a perforated ulcer of the foot, dementia, or previous hospitalization for nonhealing wounds. Patients were randomized into an experimental group with maggot dressings vs a control group with conventional dressings.

APPLICATION OF MAGGOTS

Maggots of *Lucilia sericata* were applied using a contained technique. A 2-layered bag with a small cube of spacer material within it (**Figure 1**) is filled with 80 maggots per bag (Vitapad; BioMonde Laboratories). The outer layer, directly in contact with the surface of the wound, consists of a spongy, hydrophilic polyvinyl alcohol membrane. Because of its high biocompatibility, polyvinyl alcohol is often used as a wound overlay in the healing phase and in experimental wound healing studies. The inner layer of the enclosed dressing consists of a fine nylon mesh that prevents maggots from escaping. The spacer cube, made of polyester, keeps the walls of the bag apart, increasing the space in which maggots can move, and also allows air and fluid permeability. Sterile maggots are inserted into the enclosed dressing, which is sealed with an ultrasound weld. The entire process, including packaging, is performed in accordance with the principles of Good Manufacturing Practices, and the product conforms with requirements for marketing in the European Economic Area. For each patient, the dressings were sent twice a week by air, using a 24-hour delivery service. Maggot debridement therapy was performed twice a week for 2 weeks (a total of 4 dressings per wound). Surgical debridement was not performed. One or 2 dressings were applied at each change, depending on the wound surface area. After removal of the dressing at each change, the maggots were killed with an antiseptic solution.

Control Group

Wounds of patients in the control group were surgically debrided 3 times a week with a scalpel with use of eutectic lidocaine, 2.5%/prilocaine, 2.5%, cream as topical anesthesia (EMLA, AstraZeneca) applied 30 minutes before the debridement. The end point of the debridement was the removal of slough and the appearance of red granulation tissue. Patients received hydrogel covered with a hydrocolloid dressing on dry wounds and an alginate or fiber-based dressing on oozing wounds (standard care).

Randomization and Blinding

Each patient was assigned to a group using a randomization list (stratified by center) at the Clinical Research Unit of the Centre Hospitalier Universitaire de Caen, which faxed information on the study arm to which the participant was randomized to the study center. To ensure that patients did not know which treatment was provided (single-blind design), they wore a blindfold during the dressing changes. They were also unaware of the wound care schedule (details of care and debridement procedures were not mentioned in the informed consent form), and neither group had compression applied during the 2-week hospitalization to prevent compression of the maggots. On day 1, patients were referred to 1 of the 2 centers for evaluation and treatment during a 2-week hospitalization. All patients were discharged on day 15 with hydrocolloid, hydrocellular, or alginate dressings, and a follow-up visit occurred at day 30 (**Figure 2**). Quantification of the percentage of slough and surface of the wounds was determined from photographs using a computerized planimetry software package (Canvas, version 10; ACD Systems).¹⁶

The following outcome measures for both groups were recorded from the clinical, microbiologic, and computerized picture evaluations: quantification of the percentage of slough (days 1, 8, 15, and 30), state of moisture balance (oozing/dry) of the wounds (days 1, 8, 15, and 30), wound surface area measurements to determine the percentage of healing (days 1, 8, 15, and 30), standard pain score (days 1, 8, and 15), presence of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* in bacterial swab cultures (days 1, 8, and 15), adverse effects, crawling sensations when the dressing was applied (day 8), and duration of wound care (days 1, 8, and 15).

EVALUATION OF OUTCOMES

The main outcome measurement was slough percentage at day 15, determined as slough area divided by wound area. Both areas were measured using software (Canvas) that enables the quantification of surface color in a wound after manual tracing (using a computer mouse) on a series of photographic images. Digital images were obtained and transferred to a compatible computer, using the procedure described by Laplaud et al.¹⁶ The software then calculated the circumference of the traced boundaries, the area inside the boundaries, and the percentage of slough areas within the wound. All photographs were evaluated by a single experienced nurse (B.M.) who was not involved in treatment of the patients (blinded assessment).

Secondary outcomes were also evaluated. These included wound healing; pain, measured with a visual analog scale (score range, 0-10); microbiologic swab cultures to detect MRSA and *P. aeruginosa*; and duration of wound care (time [minutes] for anesthesia, debridement, and dressing).

STATISTICAL ANALYSIS

Data were analyzed using commercial software (SPSS, version 15.0; SPSS Inc), and statistical significance was defined as $P < .05$.

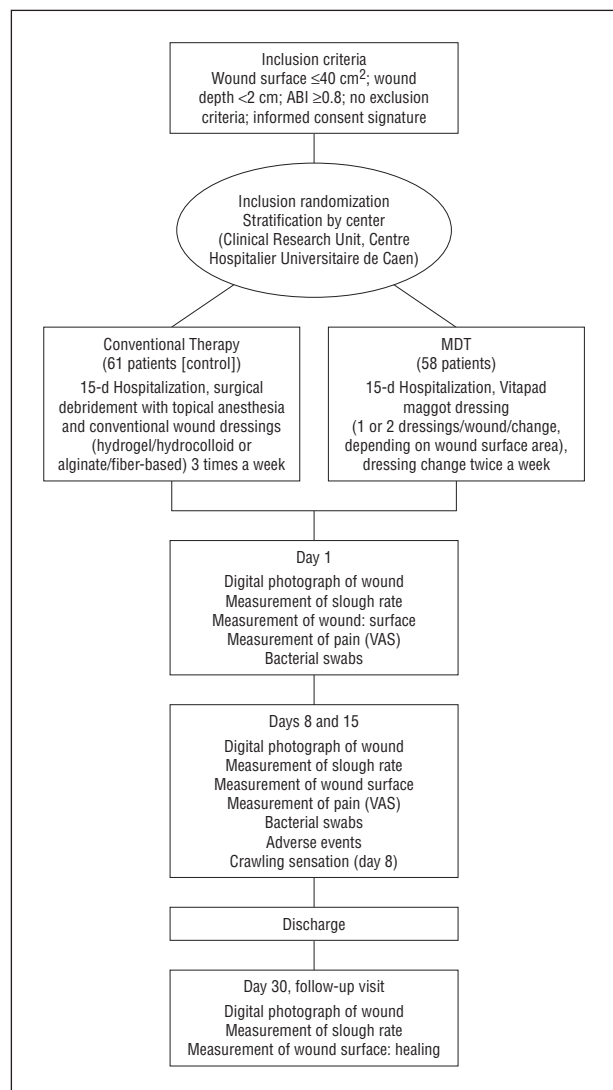


Figure 2. Trial schedule. Measurement of slough rate and wound surface was performed with computerized planimetry software. ABI indicates ankle brachial index; MDT, maggot debridement therapy; and VAS, visual analog scale.

Sample size calculation was based on the assumption of a 20% mean reduction in slough at day 15 using MDT compared with conventional therapy. With a standard deviation of the percentage of slough estimated at 37.5% of the wound surface in a small cohort of patients, a bilateral α error fixed at 5%, and a power of 80%, 55 patients per group were necessary to show a significant difference using an unpaired, 2-tailed t test. A non-parametric Mann-Whitney test was to be used to account for asymmetrical distribution of the percentage of slough; therefore, 60 patients per group were included, in accordance with the asymptotic relative efficiency of the Mann-Whitney test compared with the t test. The demographic and clinical characteristics of the patients were compared between the 2 groups, using analyses of variance for quantitative variables and χ^2 tests for qualitative variables. To assess the primary end point, a t test was used to compare the mean percentage of slough at day 15 between groups because of the symmetrical distribution of the variable. In addition, t tests were used to assess debridement at day 8 and day 30, ulcer healing, treatment-related pain, and time taken to care for the wound. For qualitative data, such as the oozing aspect of the wound, comfort of the dressing, and microbiologic modifications, χ^2 or Fisher exact tests were used.

Table 1. Patient Characteristics

Characteristic	MDT (n=51)	Control (n=54)	P Value
Age, mean (SD), y	72.8 (11.5)	73.9 (11.8)	.60
Sex, No.			
Male	22	23	.88
Female	29	31	
ABI, mean (SD)	1.1 (0.2)	1.1 (0.2)	.39
Duration of the wound, mean (SD), mo	26.9 (51.9)	18.8 (49.6)	.41

Abbreviations: ABI, ankle brachial index; MDT, maggot debridement therapy.

RESULTS

One hundred nineteen patients were randomized: 103 from Caen and 16 from Lyon. Fourteen patients were excluded. Eight of these patients did not receive the allocated intervention because they retracted their informed consent before the first treatment (1 MDT and 3 control patients) or because of the appearance of exclusion criteria between randomization and the beginning of treatment (2 MDT and 2 control patients). Five patients were excluded from analysis for lack of photographs on day 1 and/or day 15 (3 MDT and 2 control patients). One patient in the MDT group asked to stop the treatment after 6 days owing to an adverse event (grade 1 mild pain) and was consequently excluded from analysis for lack of data. A hydrocolloid dressing was applied to his wound for 48 hours, and the pain stopped.

Of the 105 patients included in the analysis, 51 received MDT and 54 received conventional treatment. There were no significant differences between the MDT and control groups (**Table 1**). The mean slough percentage was not significantly different between groups at days 1, 15, and 30. However, the difference in the slough percentage was significant between the MDT and control groups at day 8 (MDT, 54.5%; control, 66.5%; $P=.04$) (**Table 2** and **Figure 3**). Healing rates were significantly different at day 15 between the 2 groups, with a mean increase in wound surface of 14.6% in the MDT group and a mean decrease of 8.2% in the control group ($P=.02$). However, the healing rates were not significantly different between groups at day 8 and day 30 (**Table 2**). The moisture balance of the wounds remained similar for both treatments from day 1 to day 15 (**Table 3**). With pooling of the MDT and control data, the percentages of slough did not decrease significantly more at any time in oozing wounds compared with dry wounds. Pain was mild in both groups, with no significant difference in the standard pain score during dressing changes (**Table 4**). The number of infected wounds decreased from day 1 to day 15 in the MDT group but not in the control group, but the difference was not significant for either MRSA or for *P. aeruginosa* (**Table 3**). Three patients in the control group developed serious adverse events that were not related to the treatment (1 episode of leg bone osteitis and 2 deaths). Three other patients in the control group developed adverse events (hyperthyroidism, acute urinary retention, and fe-

Table 2. Slough Percentage and Wound Healing With MDT vs Conventional Treatment

Debridement	Mean (SD)		P value
	MDT	Control	
Slough, %			
Day 1	79.7 (22.3)	78.7 (23.5)	.82
Day 8	54.5 (31.6)	66.5 (25.2)	.04 ^a
Day 15	55.4 (30.0)	53.8 (33.6)	.78
Day 30 ^b	55.4 (30.4)	60.0 (36.4)	.62
Healing, %			
Wound surface, day 1, cm ²	11.5 (9.3)	11.4 (8.1)	.97
Surface decrease			
Day 1/day 8	-10.9 (38.1)	-1.5 (34.3)	.19
Day 1/day 15	-14.6 (59.6)	8.2 (37.9)	.02 ^a
Day 1/day 30 ^b	-5.3 (104.3)	12.9 (53.0)	.32

Abbreviation: MDT, maggot debridement therapy.

^aStatistically significant.

^bData missing for 3 patients in the MDT group and 11 patients in the control group.

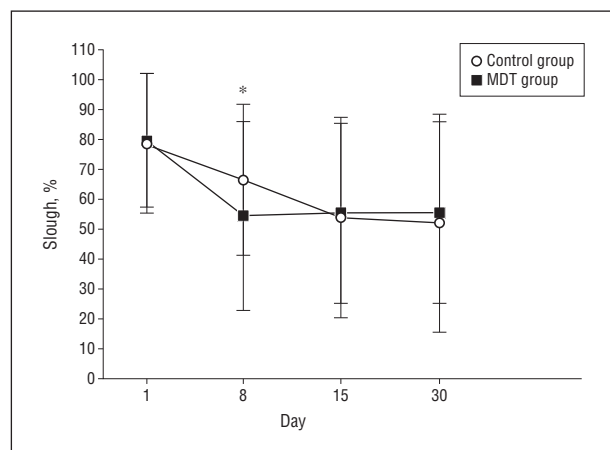


Figure 3. Percentage of slough in the wounds in the maggot debridement therapy (MDT) and control groups at days 1, 8, 15, and 30. Limit lines represent standard deviation. * $P = .04$.

caloma; periulcer eczema; and increased wound surface area with necrosis). In each group, the number of patients who had a crawling sensation on their wound at day 8 was similar. Wound care was significantly longer with conventional treatment because surgical debridement was performed with topical anesthesia applied 30 minutes before the procedure. The mean (SD) time of care in minutes at days 1, 8, and 15 was MDT, 10.1 (9.7), and control, 40.1 (8.8) ($P < .001$). Even without including the time for anesthesia, wound care was significantly longer with conventional treatment at days 1, 8, and 15: MDT, 10.1 (9.7), and control, 12.6 (8.1) ($P = .03$) (Table 4).

COMMENT

This prospective randomized trial with a blinded observer to evaluate MDT demonstrated that MDT showed no significant benefit at day 15 compared with conventional treatment. However, debridement by MDT was sig-

Table 3. Wound Characteristics

Characteristic	MDT	Control	P Value
Wound surface, day 1, mean (SD), cm ²	11.5 (9.3)	11.4 (8.1)	.97
Slough, day 1, mean (SD), %	79.7 (22.3)	78.7 (23.5)	.82
OW/all wounds, No.			
Day 1	15/51	20/54	.37
Day 8	13/51	18/54	.35
Day 15	13/51	9/54	.29
Day 30	16/51	11/54	.22
MRSA-positive swabs/all swabs, No. ^{a,b}			
Day 1	9/49	7/50	.55
Day 8	10/50	9/52	.73
Day 15	6/48	13/48	.07
PA-positive swabs/all swabs, No. ^{b,c}			
Day 1	4/50	5/50	.72
Day 8	4/51	8/52	.23
Day 15	4/49	5/48	.77

Abbreviations: MDT, maggot debridement therapy;

MRSA, methicillin-resistant *Staphylococcus aureus*; OW, oozing wounds; PA, *Pseudomonas aeruginosa*.

^aData missing for 2 patients at day 1, 1 patient at day 8, and 3 patients at day 15 in the MDT group.

^bData missing for 4 patients at day 1, 2 patients at day 8, and 6 patients at day 15 in the control group.

^cData missing for 1 patient at day 1 and 2 patients at day 15 in the MDT group.

Table 4. Wound Care and Dressing

Characteristic	Mean (SD)		P Value
	MDT	Control	
Time spent for dressing change at days 1, 8, and 15, min			
Without anesthesia	10.1 (9.7)	12.6 (8.1)	.03 ^a
With anesthesia ^b	10.1 (9.7)	40.1 (8.8)	<.001 ^a
Pain at days 1, 8, and 15, VAS (score range, 0-10)	2.3 (2.6)	2.7 (2.6)	.08
No. of patients with crawling sensation/all patients, day 8 ^c	10/49	11/49	.81

Abbreviations: MDT, maggot debridement therapy; VAS, visual analog scale.

^aStatistically significant.

^bThe anesthesia used was eutectic lidocaine, 2.5%/prilocaine, 2.5%.

^cData missing for 2 patients in the MDT group and 5 patients in the control group.

nificantly faster than in the control group during the first week of treatment, reaching the same level as the control group at day 15 (**Figure 4**). Debridement rates were not associated with the moisture balance of the wounds; therefore, a good or bad response to MDT was not isolated. The trial also confirmed that MDT does not increase healing rates. Pain scores were similar and low in both groups, but surgical debridement was performed with the use of topical anesthesia in the control group. Analysis of data collected using swabs showed no evidence of a significant difference in the presence of MRSA or *P aeruginosa* over time between the groups. Our trial demonstrated that there was no reticence to the use of MDT (all patients included were willing to have MDT). Al-

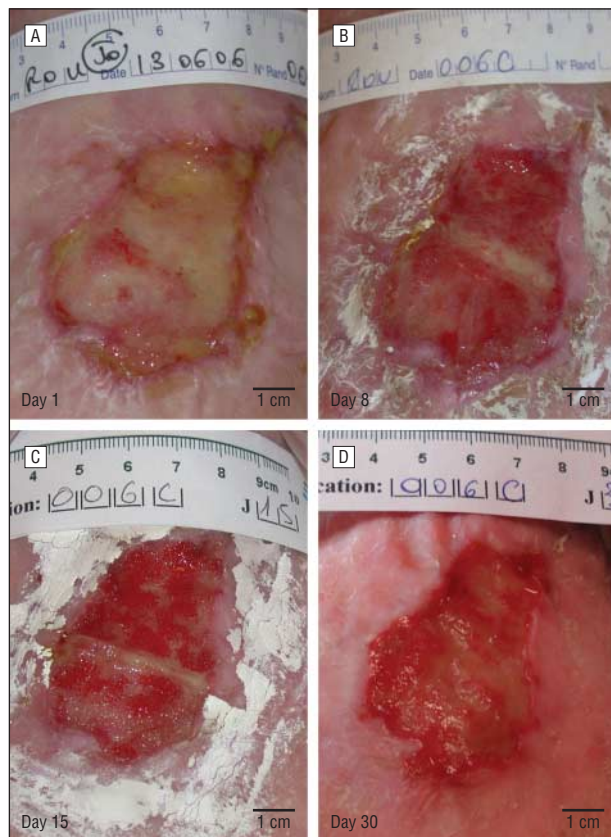


Figure 4. Healing results with maggot debridement therapy. A, A sloughy venous ulcer at day 1. B, Fast debridement achieved at day 8. C, Reduction of slough percentage at day 15. D, Appearance of the ulcer at day 30.

though the maggots were enclosed in special dressings, a crawling sensation on the wound was rarely and almost equally noted in both groups, revealing that the sensation was subjective. Nursing time was shorter in the MDT group because of the absence of topical anesthesia and scalpel debridement.

None of the previous studies^{13-15,17,18} on MDT was double-blind, given that loose larvae were used. Sherman et al¹⁴ demonstrated that most of the larval debridement occurs during the first week of therapy. Most studies^{19,20} performed with bagged larvae were open and nonrandomized. To our knowledge, only 1 prospective randomized and controlled but nonblinded trial²¹ has been conducted, in which 267 patients with venous leg ulcers received treatment with loose or bagged larvae or with hydrogel. That trial, by Dumville et al, was similar to ours, but its methods differed, with the primary outcome being time to healing and secondary outcomes being time to debridement, bacterial load, health-related quality of life, adverse events, and pain. Debridement was assessed clinically and subjectively defined as “a cosmetically clean wound.” That study,²¹ as well as a trial by Sherman,¹⁵ demonstrated that maggot-treated wounds were debrided twice as fast as wounds treated by conventional therapy in the first week of treatment. Our study, based on more rigorous methods (both treatments performed in blinded patients and outcomes evaluated by blinded assessment), confirms this observation (fast initial larval debridement persisting during the first week

of treatment but becoming much slower during the second week). Furthermore, both techniques of debridement were standardized with a 15-day hospitalization for all patients, and results were assessed with computerized planimetry software.

A previous study¹⁶ conducted in our department proved that digital image analysis is an accurate method for multicenter trials. With this precise tool, the present trial demonstrated that MDT is faster and debridement occurs within the first week of treatment. Moreover, the second week of treatment could be deleterious because a significant increase in wound surface area at day 15 in the MDT group was observed, although it was reversible at day 30 when MDT was stopped at day 15. Healing rates were not improved by MDT either in our trial or in the one of Dumville et al,²¹ in which the follow-up period was longer (median healing time, 236 days for the larvae group and 245 days for the control group). In contrast to this trial,²¹ the pain score was lower and the prevalence of MRSA was higher at baseline in our trial vs those of Dumville et al (16 of 99 vs 18 of 267). Methicillin-resistant *S aureus* was eradicated during MDT in 3 patients (9 at day 1 and 6 at day 15) but increased in the control group (7 at day 1 and 13 at day 15). In the MDT group, the number of wounds infected by MRSA decreased from day 1 to day 15, but the number of wounds infected by *P aeruginosa* remained the same. This is in accordance with previous studies²² observing that MDT seems to be more effective on wounds infected with gram-positive bacteria (*S aureus*) than gram-negative bacteria (*P aeruginosa*). This clinical difference is not the result of a direct antibacterial effect of maggots but to the 10-fold-higher dose of maggot secretions necessary to break down the *P aeruginosa* biofilms.^{9,23,24} Clinical experience and in vitro studies^{8,9} suggest that wounds heavily colonized by *P aeruginosa* should be a contraindication for MDT or should be treated with a substantially higher number of maggots or more frequent maggot dressing changes. In vivo and in vitro studies demonstrate that most of the underlying mechanisms of action of maggots can be explained by debridement of the wound bed, which includes biofilm reduction and the effect on extracellular matrix components.^{23,25} Contrary to surgical debridement, MDT is easy, safe, painless, and well accepted by the patient.

In the present study, the quality of surgical debridement was probably better (owing to hospitalization in the dermatology department and a team of nurses experienced in wound care) than that provided by community nurse-led services. This increased quality of debridement in the control group may have decreased the difference between the 2 groups. Maggot debridement therapy may be advantageous because it is not operator dependent. Although compression therapy is a best practice recommendation for wound healing, it was not applied to either group during the initial hospitalization. However, all venous ulcers in this study were included because they had not healed with compression, which was stopped during the patients' 15-day hospital stay. The absence of compression was mandatory to prevent compression of the maggots and ensure blinding of the patient. Because of the same methodologic problems, to our

knowledge, no previous study on MDT has used compression therapy. Conventional types of dressings were used in the control group. It would be interesting to perform a trial comparing MDT with polyvinyl alcohol dressings as a control group. However, we chose a comparison between MDT and optimal surgical debridement by an experienced nursing team in hospitalized patients. Because polyvinyl alcohol is not adapted to wound debridement, we decided to use conventional care dressings. Our trial was probably not long enough to evaluate complete healing, which requires several different treatment modalities. It was necessary to evaluate intermediate goals independently, such as wound debridement. Although wound debridement has not been clearly shown to speed the healing of venous ulcers in clinical studies, it is now established in the best-practice recommendations for preparing the wound bed.^{3,26,27} Also, little is known about the potential effect of topical eutectic lidocaine, 2.5%/prilocaine, 2.5%, cream on the healing process; studies^{28,29} have shown that it does not impair wound healing in animal models. However, these studies were conducted on acute surgical wounds, and specific studies should be performed in chronic wounds, as the eutectic cream is routinely used in this type of wound.

Absence of a significant difference in the presence of MRSA or *P aeruginosa* over time between groups could be partly due to the small number of patients in each group. Moreover, swabs may not be the best approach to diagnosis of wound infection because bacteria in chronic wounds mainly reside in biofilms, which prevents them from being collected on swabs and also protects them from the immune system. To ensure patients' blinding, only the enclosed dressings could be used. This methodologic issue was assumed, as the clinical effectiveness of maggots captured in bags and in free-range application is equal (confirmed in the trial of Dumville et al²¹) because their effect is not related to their crawling action on the wound surface.^{21,30} The fiber network of the enclosed dressing allows the feeding activity of larvae because it is permeable and permits migration of maggot excretions/secretions to the wound.^{31,32} The quick debridement with MDT was not dramatic but may be useful in wounds needing fast debridement; the best example of this would be wound-bed preparation for skin grafts. There is no benefit in continuing the treatment after 1 week, and MDT does not improve the time to wound closure, which is why it should be stopped when debridement is achieved. Maggot debridement therapy may also be helpful in individuals with diabetes mellitus whose wounds need rapid control, but our trial did not include this population. Further study is necessary to confirm this hypothesis, as well as a trial to determine the primary outcome assessment of microbiologic modifications.

Two questions regarding MDT remain unanswered. Can debridement be improved using more maggots per dressing? If so, would these dressings be more painful? Further studies are needed to answer these questions.

Accepted for Publication: September 29, 2011.

Published Online: December 19, 2011. doi:10.1001/archdermatol.2011.1895

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Author Contributions: Drs Opletalová and Blaizot contributed equally to the work. Dr Dompmmartin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Blaizot, Creveuil, and Dompmmartin. *Acquisition of data:* Opletalová, Chêne, Combemale, Laplaud, Sohyer-Lebreuilly, and Dompmmartin. *Analysis and interpretation of data:* Opletalová, Blaizot, Mourgeon, Chêne, Creveuil, Laplaud, and Dompmmartin. *Drafting of the manuscript:* Opletalová, Blaizot, Creveuil, and Dompmmartin. *Critical revision of the manuscript for important intellectual content:* Opletalová, Blaizot, Mourgeon, Chêne, Creveuil, Combemale, Laplaud, Sohyer-Lebreuilly, and Dompmmartin. *Statistical analysis:* Blaizot and Creveuil. *Obtained funding:* Dompmmartin. *Study supervision:* Dompmmartin.

Financial Disclosure: None reported.

Funding/Support: This study was mainly supported by Clinical Research Hospital Program grant 050345/04-130 and partly supported by a grant from the French Society of Dermatology.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, or interpretation of data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are indebted to Wim Fleischmann, MD, for sharing his experience and his advice and to Sylvie Meaume, MD (president of the French Wound Healing Society), and Brigitte Dréno, MD, PhD (professor of dermatology in the Department of Dermatology, Centre Hospitalier Universitaire de Nantes, Nantes, France), for their advice. We thank the patients and their caregivers who participated in this study, as well as the secretaries in the Department of Dermatology who provided technical and administrative assistance. Valérie Fong-Constans, BS, CLS, medical writer, revised the manuscript.

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