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A clinical study on chronic leg and foot ulcers

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Abstract
Current treatment modalities for chronic leg ulcers are time consuming, expensive, and only moderately successful. Recent data suggest that creating a subatmospheric pressure by vacuum-assisted closure therapy supports the wound healing process.
Methods: The efficacy of vacuum-assisted closure in the treatment of chronic leg ulcers was prospectively studied in D Y Patil medical college, pune with chronic leg ulcers were randomly assigned to either treatment by V.A.C. or therapy with conventional wound care techniques. The primary outcome measure was the time to complete healing (days). Statistical analysis was performed on the intention-to-treat basis.
Results: The median time to complete healing was 29 days (95% confidence interval [CI], 25.5 to 32.5) in the V.A.C. group compared with 45 days (95% CI, 36.2 to 53.8) in the control group. Further, wound bed preparation during V.A.C. therapy was also significantly shorter at 7 days (95% CI 5.7 to 8.3) than during conventional wound care at 17 days (95% CI, 10 to 2). The costs of conventional wound care were higher than those of V.A.C. Both groups showed a significant increase in quality of life at the end of therapy and a significant decrease in pain scores at the end of follow-up.
Conclusions: V.A.C. therapy should be considered as the treatment of choice for chronic leg ulcers owing to its significant advantages in the time to complete healing and wound bed preparation time compared with conventional wound care. Particularly during the preparation stage, V.A.C. therapy appears to be superior to conventional wound care techniques.

Keywords: chronic, foot, ulcers

Introduction
Chronic leg ulcers (CLUs) affect approximately 1% of the adult population in developed countries.[1] The prevalence increases with age and is estimated to be 4% to 5% in the population aged 80 years [1, 2] The course and prognosis of patients with leg ulcers differs according to the underlying pathogenesis, which is venous disease in up to 80%.[2] Several treatment modalities and protocols have been reported to date, all of them mainly focusing on ambulatory treatment of venous ulcers.[2-4] The cornerstones of these regimens are compression therapy and resolution of the cause.[2-5] It is broadly accepted now that ulcers should be débrided of necrotic and fibrous tissue to allow formation of granulation tissue, adequate epithelialization, and to decrease the chance of infection.[2-4,6]
Apart from both surgical and chemical debridement, there is not much evidence for the use of special dressings underneath the compression bandages [2-4, 7-10]. By following the currently available protocols, about 50% of ulcers will heal 4 months, about 20% do not heal 2 years, and about 8% do not even heal after 5 years [11,12]. Furthermore, various studies reported a recurrence rate after wound healing with non-operative techniques of up to 57% after 1 year [13].
The V.A.C. system exerts a controlled, local sub atmospheric pressure in the wound [16] Owing to our own promising retrospective preliminary data and the relative paucity of prospective randomized controlled trials, we started a randomized controlled trial to study the efficacy of V.A.C. in wound healing compared with standard wound dressings in hospitalized patients with recalcitrant CLU as defined in the inclusion criteria. We also evaluated the effect of V.A.C. therapy on recurrence rate, quality of life (QOL), pain, comfort, and costs of treatment [17-19]

Patients and Methods
The study was conducted at D Y Patil Medical College Pune. All patients hospitalized with chronic venous, combined venous and arterial, or micro angiopathic (arteriosclerotic) leg ulcers of 6 months' duration were eligible for entry in the study after surgical treatment options had been exhausted and extensive ambulatory treatment (6 months).
Duplex ultrasound scans of the deep and superficial venous system, an arterial work-up consisting of Doppler ultrasound scans, ankle-brachial pressure index (ABI), and transcutaneous oxygen pressure, as well as bacterial cultures were performed in all patients. In those with no apparent venous or microangiopathy arterial insufficiency but with decreased transcutaneous oxygen pressure, biopsy specimens were taken to demonstrate microangiopathy (ie, arteriosclerotic) changes.
On the basis of these findings, patients were divided into groups: (1) those with chronic venous insufficiency of the deep or superficial system without an arterial incompetence, (2) those with combined arterial and venous insufficiency of the deep or superficial system (ABI, 0.60 to 0.85), or (3) arteriosclerotic (Martorell's ulcer, biopsy proven) leg ulcers. Before inclusion in the study, underlying venous and arterial insufficiency was dealt with, and patients underwent ambulatory conservative local treatment for at least 6 months. This consisted of ambulatory debridement whenever necessary, daily or weekly (whenever necessary) cleansing with tap water, and non-adherent wound dressings creating a

controlled moist wound environment (SIGN guidelines).
Because no wound infections were observed, no topical or systemic antibiotics were used. Patients with venous or combined venous/arterial leg ulcers were treated with multilayer, short, stretch bandages. If the ulcer did not reduce in size after 6 months of ambulatory treatment, patients were hospitalized to add bed rest and skin grafting to their treatment and became eligible for entry in the study.
Patients meeting one of the exclusion criteria—ulcer chronicity 6 months duration, age 85 years old, the use of immune suppression, allergy to wound products, malignant or vasculitis origin, or ABI 0.60—were excluded from the study. In patients presenting with multiple ulcerations, the clinically most severe CLU, according to the staging system described by Falanga[21] was included in the study. Every patient was provided with trial information sheets and written informed consent was obtained. Full ethics approval from the respective local medical ethical committees was obtained, and the study was performed in accordance with guidelines set forth by the Declaration of Helsinki [22]

Procedures
Hospitalized CLU patients were randomly assigned to the V.A.C. group or to the control group (standard wound care) by a computer program using random permuted blocks of eight. Randomization was carried out within three strata, one for each ulcer type: venous, combined venous/arterial, and arteriosclerotic ulcers. Treatment allocation occurred through telephone calls to the coordinating center. In both study groups and both study centers, an initial necrosectomy was performed by sharp debridement under local anesthesia until pinpoint bleeding appeared [6].
In patients assigned to treatment with V.A.C., polyurethane ether foam was applied to the wound during the preparation stage. This foam was appropriately trimmed to fit each individual wound. A non-collapsible drainage tube embedded in the foam was connected to the V.A.C. pump; thereafter, an airtight adhesive drape was applied on top of the foam, and a permanent negative pressure of 125 mm Hg was exerted. The tube drained the wound secretion into a collection canister. In this way, a previously open wound was temporarily converted into a controlled, closed, and moist wound. A wound was considered to be prepared when granulation tissue covered 100% of the surface and wound secretion was minimal.[21]
Transplantation of full-thickness punch skin grafts was then performed. This autologous grafting, in which 4-mm superficial pieces of skin are normally taken from the thigh, was performed under local anaesthetic (Xylocaine 1%, AstraZeneca, Wilmington, Del). In conjunction with a punch graft, the skin is picked up using a rounded biopsy knife and cut off. The pieces of skin are placed on the ulcer, spaced 5-mm apart, and are covered with a no adhesive dressing, such as polyvinyl alcohol foam.
Once 100% granulation was achieved and minimal wound secretion was seen, these patients also received punch skin-graft transplantation covered with a nonadhesive dressing (Atrauman) and compression therapy. The inner dressing was not be changed for 4 days.7,21 Once all skin grafts had attached well, standard wound care was continued using a nonadhesive dressing (Atrauman) and a multilayer compression bandage (Rosidal K), when possible, until complete healing.

Statistical analysis
Data from a retrospective study showed that the mean SD duration of the 90% wound closure period was 50, 12 days in standard would care vs 31 7 days in V.A.C.17 To detect a minimal difference of 7 days in preparation time with a power of 95% (5%), the number of patients required in each treatment-group was 30, as derived from sample-size calculations. Results were analyzed on an intention-to-treat basis.
Time to complete healing (Fig 1), duration of wound bed preparation (Fig 2), and recurrence rates (Fig 3) were compared using the Kaplan-Meier survival analysis. The log-rank test was used to test for statistically significant differences between the groups. To adjust for small imbalances in the baseline distribution of relevant prognostic factors (Table I) to wound healing, multivariate analysis was performed using Cox's proportional hazards model (Table II) [13] The regression coefficient expresses the independent contribution of potential determinants to duration of cleaning and wound healing. Hazard ratios (HR) and their 95% confidence intervals (CI) are presented. P .05 was considered to be statistically significant. Percentages were compared by the 2 test, and continuous variables were compared using the independent samples t test for normally distributed variables and the two-independent sample test for non-normally distributed variables. The paired t test was used to compare QOL scores before treatment and at the end of follow-up.

Results
71 patients with 85 CLUs were hospitalized and screened for JO inclusion (Fig 4). Eleven patients with 13 ulcers were not included because they were not interested in participating. Four randomized patients (n 4 ulcers), two in the V.A.C. group and two in the control group, did not complete the protocol due to reasons mentioned in Fig 4.
In addition, one patient switched from conventional to V.A.C. therapy after 8 weeks due to an unsatisfactory therapeutic outcome. Finally, during analysis it became apparent that two patients were falsely included because they had peripheral arterial disease. Still, the therapeutic outcome in these patients was analyzed according to the intention-to-treat principle.
During follow-up, seven V.A.C. patients and four controls were lost due to reasons outlined in Fig 1. Among the 60 patients, 51 had one ulcer, six had two ulcers, and three had three ulcers (n 72 ulcers). All patients gave informed consent for inclusion in the study and were randomly allocated between the two treatment arms (Fig 4).

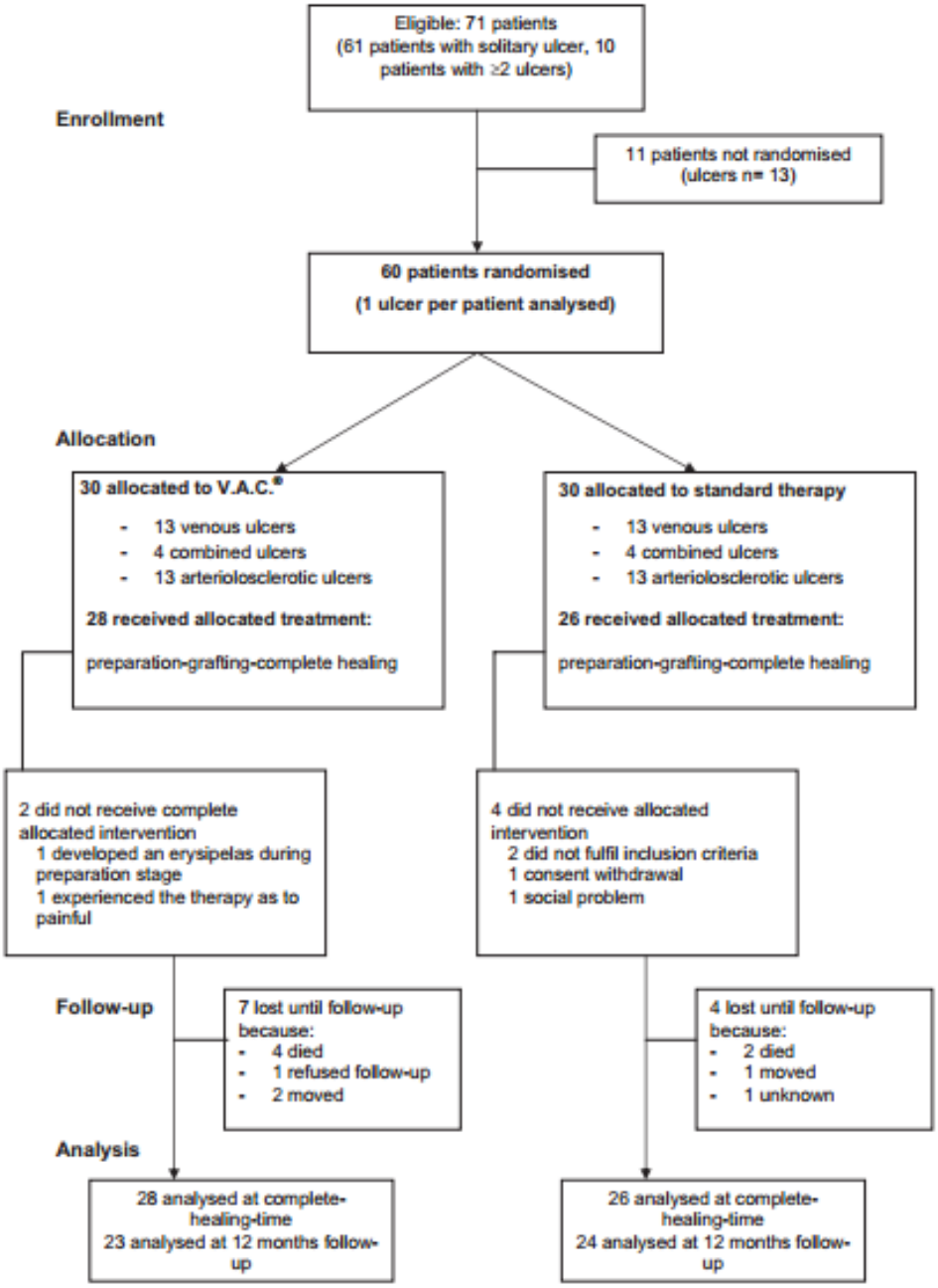

Fig 1: Time to Complete Healing (Day) In the Vacuum Assisted Closure V Wound Care.

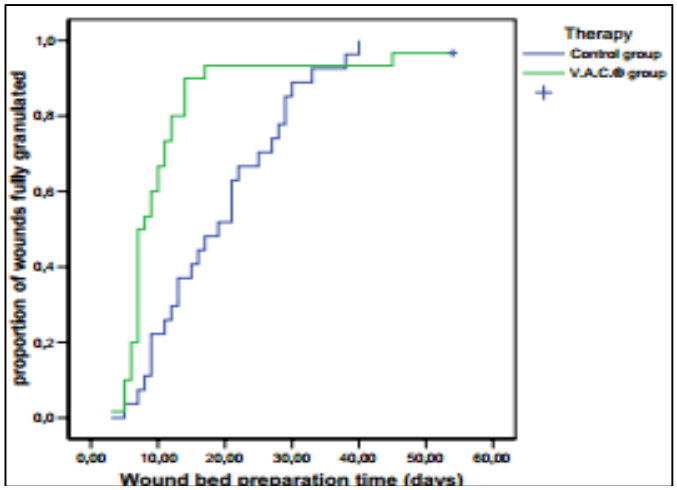

Fig 2: wound bed preparation time (day) in the vacuum-a closure (v.a.c.) Group compared with standard wound care.

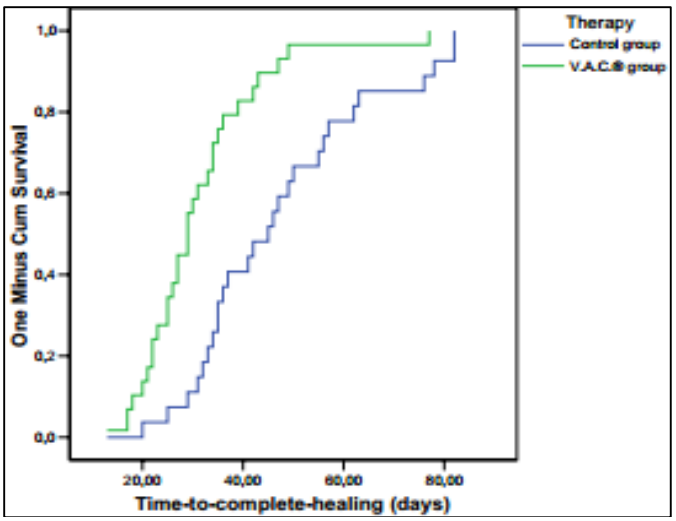

Fig 3: recurrence rate (months) in the vacuum-assisant (v.a.c.) Group compared with standard wound care.

V.A.C. therapy resulted in a significantly shorter wound bed preparation time (P .005). The median preparation time was 7 days (95% CI, 5.7 to 8.3) in the V.A.C. group vs 17 days in the control group (95% CI, 10 to 24). Moreover, 90% of the ulcers treated with V.A.C. could be cleaned within 14 days. By contrast, only 37% of the ulcers in the control group could be cleaned within this time span (Fig 2). Cox multivariate regression analysis (Table II) showed that that treatment by V.A.C. was still associated with significant faster time to complete healing (HR 3.2; 95% CI, 1.7 to 6.2) and preparation time (HR 2.4; 95% CI, 1.2 to 4.7) independently of small imbalances in prognostic factors (e.g. the ulcer surface area) to wound healing between both study groups.

Kaplan-Meier survival analysis (Fig 3, Table III) showed a median recurrence rate at month 4 (95% CI, 0.7 to 7.4) after the V.A.C. therapy vs month 2 (95% CI, 0.5 to 3.6) in the control group (P .47). After 1-year follow-up (Table III), 52% (n 12) of all healed V.A.C. ulcers relapsed compared with 42% (n 10) in the control group (P .47). All differences were not statistically significant. The median percentage of successful skin grafts (Table III) differed significantly (P .011) between the V.A.C. and control groups, with 83% 14% vs 70% 31%.

The total nursing time consumption (Table III) was significantly longer during standard wound care (386 178 minutes) than during V.A.C. therapy (232 267 minutes; P .001). There were no significant differences (P .937) between the V.A.C. and control groups with respect to time consumption for medical attention through the physician (177 76 minutes vs 181 91 minutes).

During the hospitalization period, 56 ulcers healed. Changes in QOL and in pain scores are presented in Table IV. The study groups showed significant increases in QOL at the end of therapy. During the first week, the QOL score was significantly lower in the V.A.C. group (P .031); however, this difference had already disappeared in the second week, and during follow-up, life quality was similar in both groups. With respect to pain scores, both groups showed a significant decrease at the end of follow-up, too. Comparison of pain scores revealed that the scores were initially similar during the first weeks of treatment.

From week 5 onwards, however, PPI scores were significantly lower in the V.A.C. group. Cost analysis. We have listed wound care costs in Table V. Costs for personnel were calculated on the basis of average fees for medical and nursing personnel adjusted for the clocked time spent by medical doctors and nurses with the patients. The total wound care costs for a hospitalized CLU were 25% to 30% lower for V.A.C. than for standard wound care (Mann-Whitney U test, P .001). Because we chose to keep patients hospitalized until complete healing was achieved, in contrast to normal clinical practice, we did not incorporate admission costs in the cost analysis.

Table 1: Demographic and Clinical Characteristics

	Treatment		
	*SWC (n = 30)**	*V.A.C. (n = 30)**	P
Male	7 (23)	7 (23)	NS
Female	23 (77)	23 (77)	
Age	72 (45-83)	74 (53-81)	NS†
Median ulcer chronicity at inclusion (months)	7 (6-12)	8 (6-24)	NS†
Median ulcer surface (length × width = cm^2)	43 (3-250)	33 (2-150)	NS†
Smoking	9 (30)	6 (21)	NS
Diabetes mellitus type II	5 (17)	5 (17)	NS
Immobility	13 (43)	12 (41)	NS
Hypertension	12 (40)	13 (45)	NS
No ulcer history	14 (47)	12 (40)	NS
Ulcer environment (0-4)‡	2 (0-4)	2 (0-4)	NS
Infection signs (*Pseudomonas aeruginosa*)	6 (20)	8 (28)	NS
Median ankle-brachial index (%)	100 (59-130)	100 (59-100)	NS†
Medication use			NS
Antibiotics	1 (3)	1 (4)	
Nonselective β-blockers	5 (17)	4 (15)	
ACE inhibitors	9 (30)	6 (23)	
Selective β_1-blockers	5 (17)	4 (15)	
Anticlotting therapy	7 (23)	10 (39)	
Ca^{2+} antagonists	4 (13)	1 (4)	
Ulcer type			
Venous origin	13 (43)	13 (43)	NS
CEAsP	7 (54)	9 (69)	
CEApP	6 (46)	3 (23)	
CEAdP	0	1 (8)	
Combined venous/arterial origin	4 (13)	4 (13)	NS
Arteriolosclerotic origin	13 (43)	13 (43)	NS

Table 2: Hazard Rations With 95% Congidence Intervals for Deterinant Wound Healing

	Wound bed preparation duration			Wound healing duration		
Variable	*HR*	*95% CI*	P	*HR*	*95% CI*	P
Ulcer area (cm^2)	0.56	0.29-1.09	0.09	0.5	0.25-1.01	0.058
Smoking	0.5	0.20-1.21	0.3	0.4	0.16-0.98	0.056
Infection signs	0.45	0.21-1.21	0.12	0.99	0.46-2.16	0.98
Ulcer history	1.08	0.61-1.91	0.79	0.93	0.50-1.71	0.8
Therapy	2.4	1.19-4.71	<.01*	3.22	1.66-6.21	<.000*
ACE inhibitors	1.9	0.57-2.07	0.8	0.95	0.49-1.82	0.88
Anticlotting therapy	1.03	0.53-2.01	0.92	0.69	0.35-1.38	0.3

HR, Hazard ratio; *CI*, confidence interval; *ACE*, angiotensin-converting enzyme inhibitor.
*Significant difference $P < .05$.

Discussion

Despite the development of modern diagnostic tools and remarkable therapeutic improvement, many CLUs do not heal satisfactorily in an outpatient clinic within a certain time period [2-5, 6-10] Furthermore, current treatment modalities are time consuming and expensive.2 In this study, we used a prospective and comparative study model to evaluate the efficacy of V.A.C. treatment in recalcitrant CLUs treated in an inpatient facility compared with current standard therapeutic regimens.

Our study shows that V.A.C. therapy results in a significant reduction of wound preparation time and the time to complete healing compared with common treatment modalities. Because ambulatory V.A.C. pump units are available, this treatment might be offered on an outpatient basis. Providing that patients adhere strictly to the treatment protocol and trained wound care nurses are employed, the same efficacy may be reached in an outpatient setting.

Apparently, the greatest benefit of V.A.C. in our study is reflected by a reduced median preparation time of 58% during the first time period (Fig 2). The overall complete healing time was reduced by 35% (Fig 1). These data demonstrate that V.A.C. is an extremely valuable tool in wound bed preparation. With this randomized clinical trial, we sought to assess the effect of V.A.C. therapy on wound healing in patients with recalcitrant CLU irrespective of underlying etiology. This approach may have increased the external validity of our findings, but it imposes some limitations on the interpretation of the results, especially since the number of patients is insufficient to perform subgroup analyses for each type of CLU individually.

Nevertheless, keeping in mind this limitation, V.A.C. therapy resulted in a decreased wound preparation time and total wound healing time within each CLU group (ie, venous, arteriolosclerotic, or combined venous/arterial). For the venous and arteriolosclerotic ulcers, but not for the combined venous/arterial ulcers, this difference reached statistical significance.

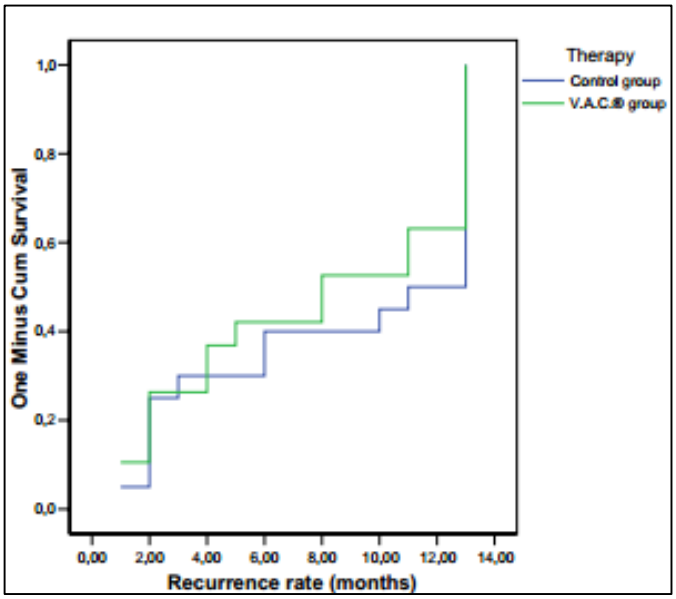

Fig 4: Trial Profile. V.A.C., Vacuum-Assisted Closure

Table 3: Secondary Outcomes

	Conventional treatment	*V.A.C.*	P
Recurrence percentage (n)	42% (10)	52% (12)	.405*
Median recurrence moment (month)	2nd	4th	.47†
Median percentage skin graft survival (SD)‡	70% (31)	83% (14)	.011§
Median wound care time (SD)			
Nurse*	330 (178)	232 (267)	.001§
Physician	181 (91)	177 (76)	.937§

V.A.C., Vacuum-assisted closure.
*χ^2 test.
†Log-rank test.
‡Significant difference $P < .05$.
§Mann-Whitney *U* test.

Conclusion

This prospective randomized controlled trial demonstrated that V.A.C. therapy leads to a significant improvement in wound management of recalcitrant CLUs. Therefore, V.A.C. therapy should be considered as the treatment of choice for CLUs. Future prospective studies with inclusion of more patients will be needed though to determine the effects of V.A.C. with respect to ulcer recurrence rates.

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