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Effective wound bed preparation using maggot debridement therapy for patients with critical limb ischaemia

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Objective: Patients with critical limb ischaemia (CLI) lack sufficient blood flow in to the limb, which leads to difficulties in the normal wound healing process. Therefore, maggot debridement therapy (MDT) has not generally been recommended for CLI patients. We evaluated the effectiveness of wound bed preparation by MDT in CLI patients who had undergone mid-foot amputation.
Methods: Patients who underwent mid-foot amputation after angioplasty between April 2014 and October 2016 were retrospectively investigated by classifying them into an MDT group or a conventional treatment group. The primary outcome was defined as achievement of wound healing. Secondary outcomes were the proportions of amputation-free survival (AFS) and successful ambulatory improvement. Propensity scores were used to evaluate treatment outcomes based on five factors: ankle-brachial index, skin perfusion pressure of the foot, nutritional status, experience with dialysis and age.
Results: A total of 39 patients (39 legs) were included, seven within the MDT group and 32 in the conventional treatment group. Clinical backgrounds of the two groups showed no significant differences except for higher albumin levels for the MDT group (3.5±0.4g/dl; p=0.014). The wound healing proportion was significantly higher in the MDT group (86%) than in the control group (38%) (p=0.035). At 6 months after amputation, no significant differences were found between the two groups for AFS (71% versus 47%; p=0.41) or ambulatory capability (43% versus 28%; p=0.65). This result was also similar to the propensity score adjustment analysis.
Conclusions: The efficacy of MDT with favourable wound bed preparation was shown in our CLI patients based on effective debridement and granulation formation by maggots, avoiding the loss of their heels. Wound-healing rates after MDT were higher for patients than for those receiving conventional treatment. MDT is considered a valid adjuvant treatment strategy for patients with CLI after revascularisation treatment is conducted. More favourable wound bed preparation and successful graft take were achieved in the MDT group, suggesting the effectiveness of MDT for wound healing in CLI patients.
Declaration of interest: The authors certify that there is no conflict of interest in relation to this article.

amputation • critical limb ischaemia • debridement • larvae • maggot debridement therapy

Maggot debridement therapy (MDT) is one of the traditional debridement methods for chronic infectious wounds using sterilised live fly larvae (maggots).[1] After an inflammatory phase, which is the second stage of a wound healing process, proteases are generated; thus, the inflammatory phase is prolonged and cannot proceed to the next stage of the healing process. Necrotic tissues not only hinder development of epithelialisation and reduction of wound size, but also they are a source of infection. Therefore, the removal of necrotic or abnormal tissues is the priority in wound bed preparation, including cleansing and debridement of the wound.[2] In addition, critical colonisation or infection tends to occur in wounds with poor autonomic healing ability, leading to the need for prompt and effective debridement.

There are four major methods of debridement considered for selective removal of necrotic tissue: surgical, enzymatic, autolytic, and biological (namely, MDT). Surgical debridement removes necrotic tissues with scissors or scalpel, which entails bleeding and pain for patients and, to some extent, damage to peripheral intact tissue. Enzymatic or chemical debridement involves the use of chemical agents which liquify necrotic tissues. This can be done without anaesthesia and is relatively simple to perform with little risk of bleeding; however, it is a time-consuming procedure and thus not suitable for situations requiring more immediate results. Autolytic debridement involves the application of wound dressing materials, such as ointments or hydrocolloid materials, making the treatment suitable for wounds located near the body surface or the autonomic healing power of the wound is viable. Finally, there is biological debridement with MDT.

Wound healing is intractable in most critical limb ischemia (CLI) patients who have reduced blood flow to the limb; thus, revascularisation is considered the most important factor for successful management. Further, the debridement of wounds with no sufficient

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Table 1. Patient characteristics

Variables	Level	MDT Group (n=7)	Control Group (n=32)	p-value
Age (years)		73.6±6.1	69.7 ±1 1.3	0.38
Sex	Male	5 (71%)	25 (78%)	0.65
Body mass index (kg/m²)		22.3±4.2	19.7 ± 3.5	0.096
Diabetes	Yes	7 (100%)	22 (69%)	0.16
Hypertension	Yes	7 (100%)	30 (94%)	1.00
Dialysis	Yes	6 (86%)	27 (84%)	1.00
Cardiac disease	Yes	5 (71%)	24 (75%)	1.00
ABI of injured leg		1.0±0.3	0.9±0.3	0.33
SPP of the dorsum (mmHg)		35±17	42±23	0.47
SPP of the plantar (mmHg)		35±22	43±22	0.37
Ambulation before surgery	Yes	6 (86%)	21 (66%)	0.40
Ejection fraction (%)		47.1±16.2	50.3±14.5	0.61
Amputated level	Transmetatarsal amputation	5 (71%)	23 (72%)	1.00
	Chopart's joint amputation	1 (14%)	6 (19%)	
	Lisfranc's joint amputation	1 (14%)	3 (9%)	
Right limb injury	Yes	2 (29%)	20 (63%)	0.21
Nutrition condition	Normal	2 (29%)	7 (22%)	1.00
	At risk of malnutrition	4 (57%)	17 (53%)	
	Malnourished	1 (14%)	8 (25%)	
Albumin (g/dl)		3.5±0.4	3.0±0.5	0.014
WBC count (/µl)		7087±2300	8751±3379	0.22
CRP (g/dl)		1.83 [1.40, 6.60]	4.49 [1.65, 7.80]	0.42
HbA1c (%)		6.4±1.2	6.4±1.4	0.90

MDT—maggot debridement therapy; ABI—ankle-brachial index; SPP—skin perfusion pressure; WBC—white blood cell; CRP–C-reactive protein; Data are reported as mean±standard deviation or median [quantile 1, quantile 3] for continuous variables. P values were assessed by Student's t-test or Wilcoxon's rank sum test for continuous variables and Fisher's exact test for categorical variables

tissue blood flow may deteriorate ischaemic lesions.[2] Therefore, in general surgical treatments, including MDT, have not been recommended for ischaemic limbs.[3] Also, surgical debridement at the bedside is often difficult due to unclear margins between the necrotic and granulated tissue, and the possibility of severe pain to the CLI patient.

In this study, we investigated MDT in CLI patients who underwent mid-foot amputation after revascularisation by endovascular therapy (EVT), comparing the outcomes of wound bed preparation (wound bed preparation) with those receiving conventional therapy.

Methods

Study population

Our subjects were a consecutive series of CLI patients whose wounds appeared not clean enough to be closed after mid-foot amputation in our institution between January 2013 and October 2016. Patients for whom the wound remained open due to poor wound bed preparation with a resulting direct major amputation were included. All of our subjects underwent preoperative revascularisation by EVT. We retrospectively investigated age, gender, clinical history, experience of dialysis, ankle-brachial index (ABI), skin perfusion pressure (SPP), blood test results (including white blood cell count, levels of C-reactive protein, albumin, and HbA1c), nutrition status, ejection fraction, and ambulatory status before hospitalisation, based on archived medical data at our institution, and compared the data of the MDT and control groups.

Definitions

In our study, wound bed preparation of conventional therapy (control group) indicates application of ointment once or twice daily after cleansing the open wound after surgery. We used sulfadiazine silver or bromelain ointment on necrotic tissues. In cases of maceration or where wounds infection signs of were observed, we used povidone-iodine ointment. When remaining necrotic tissue was observed after these conservative treatments, surgical debridement was conducted either under local anaesthesia (lidocaine injection) or surface anaesthesia (lidocaine hydrochloride jelly). However, as there are no standardised protocols, wound bed preparation was initiated by the treating surgeons based on their decisions. In cases presenting favourable granulation, skin graft was conducted 2–4 weeks after the initial surgery.

Table 2. Outcomes at six months after mid-foot amputation by adjusted and unadjusted analysis

Outcomes at 6 months after midfoot amputation	Unadjusted analysis			Adjusted analysis			
	MDT group	Control group	p-value†	MDT group	Control group	OR (95% CI)	p-value‡
Wound healing	6 (86%)	12 (38%)	0.035	90.1%	33.4%	18.10 (1.41–232.98)	0.026
AFS	5 (71%)	15 (47%)	0.410	77.5%	43.4%	4.51 (0.62–32.63)	0.140
Ambulation	3 (43%)	9 (28%)	0.650	51.7%	22.5%	3.69 (0.54–25.15)	0.180

MDT—maggot debridement group; AFS—amputation-free survival; OR—odds ratio; CI—confidence interval;
Note: wound healing was defined as the state in which healing was achieved with avoidance of major amputation; †p-value for group-comparison by Fisher's exact test; ‡p-value for group-comparison by the adjusted analysis based on propensity score

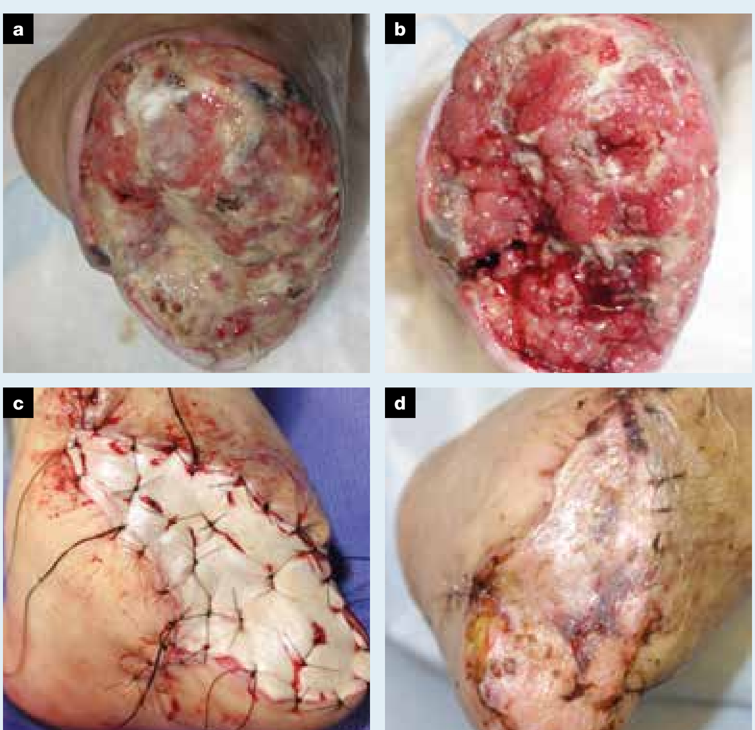
MDT was conducted on patients for whom conventional therapy failed to achieve successful healing. After cleansing the wounds and removing biofilms or ointment from the amputated surface, a hydrochloride patch (DuoActive, ConvaTec Inc, Tokyo) was applied trimmed to the shape of the lesion for prevention of maceration in the wound periphery and the escape of maggots.

Sterile grown maggots for medical use were purchased from the Japan Maggot Company, Inc. (Okayama, Japan). Second instar larvae of maggots were placed on the ulcerated surface at 10 larvae per 1cm^2, and covered with a nylon mesh sheet. A 48-hour duration was defined as one session. MDT was terminated either when favourable wound bed preparation was achieved to the extent of being ready for skin graft, or when there was no notable effectiveness of MDT. In cases with favourable wound bed preparation, a skin graft was performed at one week after termination of MDT. In both groups, the treated foot remained elevated for approximately 10 days after a skin graft; then, activities of daily living (ADL) were gradually increased dependent on the condition of the wound.

Postoperative wound healing was defined as the condition in which the skin graft was taken and surgical intervention with hospitalisation was considered unnecessary. Ambulation was defined as being capable of walking without another person's assistance, regardless of the distance or use of a walker tool. 'Mid-foot amputation was defined as either a transmetatarsal, Chopart's joint or Lisfranc's joint amputation. For evaluation of nutritional status a 'mini nutritional assessment (MNA)'[4] was used for patients ≥65 years of age and 'malnutrition universal screening tool (MUST)'[5] was used for patients >65 years. The evaluated results were classified into:

- Normal nutritional status
- At risk of malnutrition
- Malnourished.

Fig 1. Outcomes after transmetatarsal amputation (72-year-old man). Three weeks after transmetatarsal amputation, yellowish necrosis is seen on the amputated surface of the left leg (**a**). After one session of maggot debridement therapy, reduction of necrotic tissues and granulation formation are seen (**b**). Intraoperative view of skin graft conducted after three sessions of maggot debridement therapy (**c**). One month after dermatoplasty, the grafted skin has taken and favourable epithelialisation was achieved (**d**)



Evaluation of outcomes and study endpoints

The primary outcome of our study was the proportion of wound healing without major amputation. The secondary outcomes were the proportions of amputation-free survival (AFS) and capability of ambulation. All outcomes were assessed by the same experienced plastic surgeon as an open-label (unblind) study at 6 months after surgery. Outcome findings were investigated at inpatient or outpatient consultation by observing and questioning the patient's condition. In cases where the patient moved to another area or it became difficult for the patient to visit our institution periodically, we made telephone calls to the new treating doctor or the patient's family member to request information on the patient's condition. All information was obtained from the medical archives of the New Tokyo Hospital.

Statistical analysis

No data were excluded from any analyses. Categorical data were summarised as the frequency (%) and continuous data were expressed as the mean and standard deviation (SD) or median and the interquartile range (between quartile 1, Q1 and quartile 3, Q3). Group comparisons between maggot and control groups were performed by using Fisher's exact test for categorical variables and Student's t-test or Wilcoxon's rank sum test for continuous variables. To determine the maggot effect on the primary and secondary outcomes, we estimated the odds ratio (OR) and its 95% confidence intervals (CI) based on the propensity score adjustment. The propensity score was calculated by a logistic regression model, including ABI, dorsal SPP, plantar SPP, nutrition status, haemodialysis and age as covariates (known as prognostic factors).[6] All statistical analysis were performed using SAS 9.4 (SAS Institute, Cary, US). A value of $p<0.05$ was considered significant.

Results

Our study included 39 consecutive patients, their demographic data is presented in Table 1. Clinical backgrounds of the MDT group (seven patients) and control group (32 patients) showed no significant differences except for higher albumin levels in the MDT group (3.5±0.4g/dl) compared with the control group (3.0±0.5; p=0.014). Also, no significant difference was found regarding the comprehensive nutrition evaluation (based on MNA or MUST).

Outcomes

The proportion of wound healing that avoided major amputation was significantly higher in the MDT group (86%) compared with the control group (38%; p=0.035); although AFS at 6 months after surgery (p=0.41) and proportion of postoperative ambulation (p=0.65) showed no significant differences between the groups (Table 2).

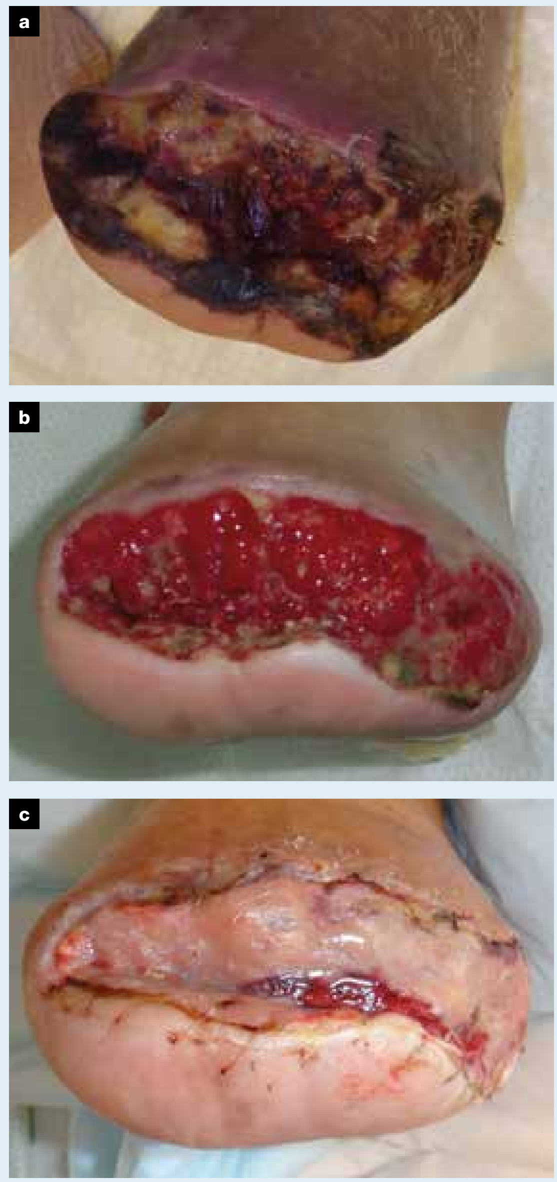
Also, propensity score analysis showed a significantly higher wound healing proportion for the MDT group (90.1%) compared with the control group (33.4%) [p=0.026; OR: 18.10; 95% CI: 1.41–232.98]. The OR of AFS 6 months postoperatively was 4.51 [95% CI: 0.62–32.63] (p=0.14) and postoperative ambulation was 3.69 [95% CI: 0.54 to 25.15] (p=0.18) (Table 2).

Pain control with oral non-steroidal anti-inflammatory drug (NSAID) administration was used in all subjects of the MDT group. In most of the patients in the control group, pain control was possible with oral NSAIDs; however, for patients with a severe pain, we used intravenous NSAIDs or lidocaine hydrochloride jelly before surgical debridement. Representative MDT cases with favourable wound bed preparation results are presented below.

Case 1

A 72-year-old male presented with ischaemic necrosis and infection in the his toes. ABI before angioplasty was 0.68, and angiography showed 99% stenosis of the anterior tibial artery. After conducting balloon angioplasty, ABI improved to 0.99, thus transmetatarsal amputation was performed. However, yellowish necrosis and signs of infection on the amputated surface after conventional treatment resulted in the use of MDT (Fig 1a). After one session (48 hours) of MDT, the surface yellowish necrosis diminished and granulation formation was noted (Fig 1b). Skin graft was conducted after two MDT sessions (Fig 1c). All the

Fig 2. Outcomes after transmetatarsal amputation (75-year-old man). After three weeks of transmetatarsal amputation, black and yellowish necroses are seen on the amputated surface (**a**). After three sessions of maggot debridement therapy, reduction of necrotic tissues, granulation formation, and reduced lesion size are seen (**b**). One month after surgery. Approximately, 85% of the skin graft was taken (**c**)



skin grafts were taken, epithelialisation was achieved, and ambulation was possible at one month after dermatoplasty (Fig 1d).

Case 2

A 75-year-old man presented with ischaemic necrosis of the left toes. Angiography showed 90% stenosis of the anterior tibial artery, and chronic total occlusion was seen in the posterior tibial artery. As restenosis occurred repeatedly, EVT was conducted three times to each lesion. After improvement of ABI to 1.01, TMA was performed. However, delayed wound healing of the amputated surface was noted, thus MDT was conducted at 3 weeks after surgery (Fig 2a). After three sessions of MDT, black (and partly yellowish) necrosis on the wound surface reduced substantially, and granulation formation and reduction of the wound size were seen (Fig 2b). Approximately 85% of the skin graft was taken at one month after surgery (Fig 2c).

Discussion

In patients with CLI, wound bed preparation is often difficult to be achieved due to insufficient blood flow to peripheral tissues, which hinders normal process of healing mechanisms. Fleishmann et al. reported efficacy of MDT for their 123 patients with acute or chronic infections and chronic wounds, although the worst results were seen in chronic arterial occlusive disease.[3] We also consider that sufficient arterial supply is an important factor for CLI patients. In clinical practice, however, we often encounter patients who cannot achieve favourable wound healing in spite of an improved ABI after revascularisation. Even when patency of the main artery of the lower limb is acceptable, blood flow sometimes does not reach to the peripheral capillary vessels, which hinders granulation formation. In such cases, although necrosis does not instantly progress as a certain blood flow is maintained, the wound healing process stagnates. This is the reason why the treatment selection becomes unclear in some cases.

There are three major benefits of wound bed preparation by MDT for CLI patients.[7–9] First, selective and efficient debridement is possible. Even for wounds with unclear margins with the surrounding normal tissues, maggots selectively englobe and liquefy only necrotic tissues.[10] In addition, as maggots naturally favour darker environments (negative phototaxis), maggots reach to the deeper portions of a wound where surgical debridement is difficult. A maggot eats an amount equivalent to half their weight in 5 minutes, which translates to 25mg of necrotic tissues within 24 hours per maggot.[11] Pain associated with MDT can be controlled either with oral analgesics or by adjusting the number of applied maggots, making local or surface anaesthesia unnecessary.[12] Further, the technique for MDT is relatively straightforward and easily learned, minimising the need of special training for effective application. The use of MDT may be feasible for the increasing number of patients of advanced age, and those with dementia or unfavourable systemic conditions, for whom surgical debridement is impractical.

The second benefit is promotion of granulation formation with MDT.[13] Protease, primarily serine protease in maggot excretion/secretion, has an ability to produce hepatocyte growth factor (HGF), and HGF production is strongly enhanced through activation of transcription factors, such as 'Stat 3' which is located under cMET, a receptor of HCG.[14] In addition, activation of HCG is related to the migration of endovascular cells through the PI3K/AKT pathway.[15] Nigam et al. reported that maggot secretions promote the cellular processes that are related to this increased healing activity.[8] Such processes include activation of fibroblast migration, angiogenesis (formation of new blood vessels from pre-existing vessels) within the wound bed, and an enhanced production of growth factors within the wound environment.[8,9] A recent case report, in addition to supporting its effectiveness for debridement, also indicated the possibility that MDT improves blood flow, showing increased skin perfusion pressure by 42mmHg in the dorsum and 27mmHg in the plantar.[16] In the present study, after revascularisation by EVT, average ABI and SPP improved to be greater than 0.9 and 30mmHg, respectively, which were considered causes for favourable outcome after MDT with generation of capillary vessels and reduction of vascular resistance.

The third benefit is the antibacterial action associated with MDT. Maggots have a sterilising effect both *in vivo* and *in vitro*. In the body, maggots eliminate bacteria through digestion in the foregut, midgut and hindgut of their alimentary tract.[11] In an extracorporeal *in vitro* study, antibacterial peptide contained in maggots' secretion was shown to be effective against Gram-positive bacterium, including meticillin-resistant *Staphylococcus aureus* (MRSA).[17] Thus, MDT is considered suitable for CLI patients who have multiple drug-resistant bacteria at the wound site, suggesting a relative high level of immune deficiency and a risk of long-term hospitalisation.

In our results, wound healing was more favourable in the MDT group than the control group. Landry et al. reported healing was achieved in 33 of 62 legs undergoing TMA (including those without CLI), and, when excluding seven subjects who died during the perioperative period the healing rate was approximately 60%.[18] Stone et al. reported healing was confirmed in 57 of 73 subjects (78%) who underwent midfoot amputation (excluding those who died during the perioperative period).[19] Although we cannot directly compare our results with the reported results due to the differences in patient background, evaluators, and procedures, we believe the higher wound healing rate (86%) for our MDT group is promising.

However, our study results did not show significant differences of AFS at 6 months between the MDT and conventional groups. Landry et al. reported that the prognostic mortality rate was not significantly different between groups healed after TMA and not healed, but the presence of renal failure which necessitate dialysis was an important factor [OR:, 4.85; 95% CI: 1.01–23.30, p=0.047].[18] Shiraki et al. mentioned that definitive factors for prognosis of CLI patients after angioplasty were age (>75 years), dialysis, reduced cardiac function (ejection fraction< 50%) and with no ambulation.[20] Therefore, the reason for no significant AFS difference in our two groups may be due to the absence of any significant differences in their clinical backgrounds.

Regarding achievement of ambulation in patients healed after TMA, Landry et al. reported 73%,[18] and Stone et al. reported 92%;[19] thus, the success rate for our MDT group (43%) must be considered low. One major reason for this low figure is likely that, because MDT is not covered by the Japanese national health insurance system, the only patients seeking MDT are those with severe disease where conventional treatments have not yielded favourable outcomes. The average age of our MDT group was 73.6 years, and muscle strength and vitality were diminished due to extended periods of hospitalisation, which led to a reduction of ADL even after wound healing.

Limitations

Limitations of our study include a small number of patients at a single institution. Another limitation was that MDT was conducted as a non-insured practice and our investigation was retrospective, which indicates that the treating surgeon had selected MDT candidates as 'legs which appeared to heal by MDT'. To overcome these limitations, we assessed the outcomes by adjusting for backgrounds as far as possible, based on propensity scores (Table 2). The tendency of the adjusted results was similar to that without adjustment; thus, our findings are considered to remain reasonable. For a more accurate and objective evaluation of the MDT effect, accumulation of patient data by a prospective randomised controlled trial is desired in the future.

Conclusion

The efficacy of MDT was shown with our CLI patients who underwent angioplasty and mid-foot amputation, and for whom wound bed preparation by conventional treatment was difficult. Wound-healing rates after MDT was higher than that after conventional treatment. MDT is considered a valid adjuvant treatment strategy for CLI patients with a certain improvement of blood flow after revascularisation. **JWC**

Reflective questions

- Would you consider using maggot debridement therapy (MDT) in your practice
- What different mechanisms of debridement have you used in the past and who do these compare with MDT
- Have you used the mini nutritional assessment (MNA), malnutrition universal screening tool or a simialar tool?

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