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Case Report

# Localized Treatment of Chronic Buruli Ulcer with Hyperoil™: An Unexpected Outcome

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## Abstract

The successful sustained outcome of this patient with chronic Buruli Ulcer treated with Hyperoil™, suggests its use for local treatment of infected ulcers with bone exposition. Hyperoil™ use could be particularly effective in endemic areas, far from specialized centers, where African populations living in poor rural areas are more difficult to be treated.

**Keywords:** Chronic Buruli ulcer; Buruli ulcer local treatment; Osteomyelitis; Infected cutaneous ulcer

## Background

Buruli Ulcer (BU) is an extensive tissue necrosis resulting from an initial skin infection caused by a diffusible lipid toxin (mycolactone) produced by *Mycobacterium ulcerans*, a bacterium prevalent in humid, rural tropical areas. Several thousand people are infected each year, especially in tropical Africa, where BUs are often a source of major disability, especially linked with super-infections [1]. As little is known about disease transmission, prevention is difficult. Furthermore, even if several studies are in progress, to date, there is no vaccine [1]. A combination of oral rifampicin and injectable streptomycin is the treatment recommended by World Health Organization [2,3], in early, limited disease [4], but in a few cases in the deep and remote lands, because of the lack medicines, it is not possible use antibiotics [5]. As not all patients with M. ulcerans infection have BU, the synergistic anti-mycobacterial action of antibiotics and immune defense mechanisms may be required to treat the infection efficiently [6]. The differential diagnosis of BU due to *M. ulcerans,* based on clinical and epidemiologic basis only, is difficult [3], so the BU diagnosis needs to be confirmed by IS2404 polymerase chain reaction (PCR) [7].

Surgical treatment and functional rehabilitation are often necessary but their use and the best time for surgery for large BUs needs clarification [3]. High relapse rates [8], prohibitive cost and limited access to surgery in endemic areas in Africa (far from National reference centers for BU treatment) led to search new therapeutic options being easily used by local health care providers in these poorly assisted areas. Some BUs can become chronic as not fully recovered because of inappropriate treatment, or even using reference treatments, that led to infection [9].

Members of the no-profit organization Helios Med periodically go to Ariwara (Congo Democratic Republic, Africa), for training missions to local health care providers working in the surgical clinic. Chronic BU is an endemic pathology in Congo DR, especially in younger population of the most isolated zones. The presence of M. ulcerans was confirmed with Zihel Nielsen method performed in the laboratory equipped by Inter Med Onlus.

Trainings include the antiseptic treatment of the wounds with ozone therapy, being the standard protocol applied for the treatment of BU [9]. During our last mission, on July 2012, the ozone production unit stopped working and, thus, we were obliged to find an alternative wounds local treatment.

The only available antiseptic we had was Hyperoil™, a mixture of hypericum flowers extract (*Hypericum perforatum*) and nimh oil (*Azadirachta indica*) produced by RIMOS S.r.L. Mirandola (MO) - Italy (Medical Device Class IIB CE0476), available as oil, gel, cream and gauze gel, that was recently tested to be used in complicated diabetic foot ulcers [10].

## Case Presentation

We used Hyperoil™ on a 13 years old boy with chronic BU at the bottom right leg and osteomyelitis. Chronic BU was located at the lateral bottom middle third of the right leg and on the upper pole (at about 4 cm from the perilesional cephalic margin), and appeared about 15 months before. The patient refers the lesion started as a painful nodule on the leg that become edematous. Then, the skin above the nodule ulcerated with white-yellow material in the middle of the lesion, having cotton appearance. The lesion become larger and deeper in the next days. This patient was previously treated with an unknown antibiotic therapy and his ulcer had a surgical toilette, with temporary improvement of symptoms. Then, because of the lack of money to continue treatments, BU worsened in the following year.

On September 19th 2012, when the boy was visited by us for the first time, a chronic BU (13.5x5 cm, Figure 1A) appeared localized, exuding and smelly, with focal exposed bone necrosis on two sites (depth, respectively, 0.3 mm and 1 cm) in a limited area healed, with slight scar retraction, in the third distal area of the right leg (approximately 4 cm from the cephalic peri-lesional margin). The ulcer was delimited by partially regular and undermined edges, skin




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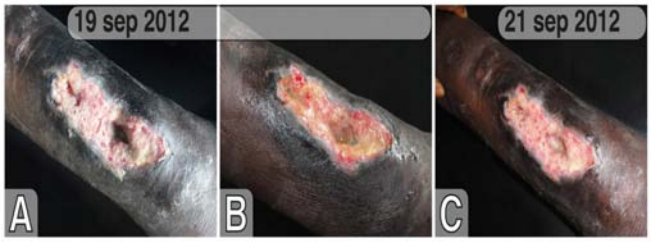


**Figure 1:** Chronic Buruli Ulcer before starting treatment with Hyperoil™ (A). The first application Hyperoil™ oil (B) on September 19th 2012 and after 2 days (C) on September 21st 2012.

being scarcely elastic and edematous in the area around the lesion.

Two areas in the lesion (1 cmq and 3 cmq, respectively) showed exposed periosteal with bony fragment necrosis of the tissue. The bottom of the ulcer was strength fibrous. The peripheral cutaneous tissue of the ulcer was hyper-keratotic, dystrophic, hyper-chromic and with some necrosis.

The patient needed to use a walking stick and feel pain (VAS score = 5).

The clinical anamnesis and objective evaluation confirm the diagnosis of chronic BU.

## Management

This wound was treated with Hyperoil™ oil applications (Figure 1B) on any other day. The skin around the wound was carefully cleaned with normal Ringer solution and gauze having a few drops of Hyperoil™ oil. The ulcer's bed and undermined edges were, than, cleaned, as, exudates and fibrin residuals or necrotic materials were removed, with a gauze with Hyperoil™. Then, a little Hyperoil™ oil was dropped in the ulcer including exposed bone. In addition, ulcer was covered with gauze and bended to maintain dressing in the appropriate zone and let the ulcer cleaned from dust. Surprisingly, 2 days after the first application of Hyperoil™ skin hyperchromia was reduced, lesion edges and ulcer fundus showed an improvement of cutaneous tropism (Figure 1C).

Necrosis was completely cleaned after the first week of therapy (on September 26th 2012) and chronic BU showed a partial reduction of fibrin with the appearance of granulation tissue (Figure 2A).

After 2 weeks, the bone turned to be covered (Figure 2B); the granulation tissue was well represented on the whole area of the ulcer. Peri-lesional edges were no more undermined. The ulcered area was reduced and the wound become superficial. The patient was able to walk without any aim and pain disappeared (VAS = 0).

Eighteen days after starting Hyperoil™ treatment, new epithelium appeared on the lower pole of the lesion, and new skin appeared when medication was substituted (Figure 3A).

After 3 weeks, the ulcer continued to reduce its hyperchromy and it had no decolorized or cicatrized areas (Figure 3B). This was a surprising outcome.

One month later, on October 18th 2012, the ulcer was completely healed (Figure 3C) without scar retraction.

The absence of relapse was confirmed by a phone follow-up call,

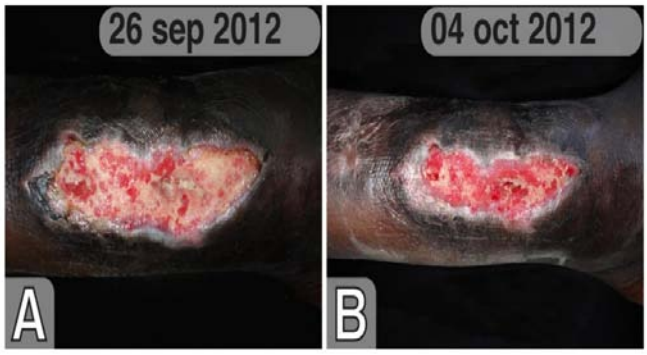


**Figure 2:** Chronic Buruli Ulcer after 1 week (A) and 2 weeks (B) of treatment with Hyperoil™.


**Figure 3:** Chronic Buruli Ulcer after 18 days (A), 3 (B) and 4 (C) weeks of treatment with Hyperoil™.

with a local physician, on May 2014.

The patient gave his consent to publish the results of this case.

## Discussion

Chronic BU remains a serious health issue especially where WHO recommendations are difficult or cannot be applied due to severe poverty and geographical isolation [9].

The differential diagnosis of BU needs to be confirmed by Ziehl-Neelsen (ZN) staining [11] and PCR [7]. Diagnostic tests are suitable for use in primary care settings but these are difficult to be performed in the most isolated zones. Often, but not in our case, diagnosis has to be performed on a clinical basis, only.

Antibiotic therapy, recommended by WHO, is really effective even at long term [12,13], but is relatively expensive and, in some cases, difficult to be reached especially in the most poor and remote endemic areas of BU, where traditional poorly-effective remedies remain a frequent choice [14]. In these areas the recommended surgical approach is difficult to be applied, too, due to the lack of or the difficulty to access to hospitals [14].

Having a cheap and simple-to-be-transported therapeutic option, as Hyperoil™ to treat patients with chronic BU, could give to local well trained health care providers a new topical local treatment. This approach to the patient with chronic BU, including health education [15], could permit BU treatment and control.

## Conclusion

Despite not having PCR confirmation of the diagnosis of BU, the unexpected recovery of this patient treated with Hyperoil™ opens a new perspective for the future of local chronic BU treatment.

Properly designed, controlled trials are needed to confirm this first observation.

## Acknowledgment

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Case Report

# A Case of Skin Ulcer in Severe Acute Malnutrition Treated with Hyperoil®

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**Abstract**

A 3 years old baby with complicated SAM and extended exudating, smelling, advanced and infected lesions on both lower legs has been treated with Hyperoil Mgel gauzes at NRC. Surprisingly, in few days her trophic lesions recovered avoiding keloids and cutaneous discoloration.

**Keywords:** Severe acute malnutrition; Edema; Kwashiorkor; Skin ulcer; Child; Hyperoil®

## Background

Malnutrition is complex condition which has social repercussions and is associated with medical disorders [1].

In Sub-Saharan Africa, malnutrition is a relevant emergency, directly or indirectly responsible for 35% of child mortality [2].

According to the World Health Organization (WHO) standards, SAM in 6-60 months old infants and children is defined by a very low weight for height (below -3z scores of the median WHO growth standards), by visible severe wasting (Mid-Upper Arm Circumference (MUAC) less than 115 mm), or by the presence of nutritional edema (clinical sign). These standards are appropriate for infants and children of different ethnic groups.

SAM is characterized by edema, irritability, anorexia, ulcerating dermatoses, and an enlarged liver with fatty infiltrates. Sufficient calorie intake, but with insufficient protein consumption, distinguishes it from Moderate Acute Malnutrition (MAM, below -2z scores of the median WHO growth standards). MAM rapidly improves, whereas children affected by SAM are apathetic, with swollen abdomen, and have a poorly responsive immune system [1].

Generally, SAM can be treated by adding protein to the diet; however, it can have a long-term impact on a children's physical and mental development and they can fall victim to untreatable infections and that, in severe cases, might lead to mortality. In fact, two types of Protein-Energy Malnutrition (PEM) have been described: kwashiorkor and marasmus. Kwashiorkor occurs with fair or adequate calorie intake but inadequate protein intake, whereas marasmus occurs when the diet is inadequate in both calorie and protein intakes [3].

Children having SAM or MAM, defined according with WHO standards, are followed and treated at the Nutritional Recovery Centre (NRC) run by the P.M.I. "Filles de St. Camille" in Zinviè (Benin) and supported by Helios Med and InterMed in educating and treating malnutrition, in order to reduce its their impact on child mortality.

The staff of Helios Med and InterMed, two Italian non-profit international health organizations, uses to go periodically to Zinviè where they built up a wound care centre and in their short missions train local health care providers working there. Training includes the preparation of ozonated water by bubbling $O_2$-$O_3$ in a 2,000 ml glass bottle for five minutes at the concentration of 30 µg/ml to clean ulcer bed and perilesional area; antiseptic treatment of the wounds with ozone therapy, being the standard protocol applied for the treatment of Buruli Ulcer [4]. Since 2013 they introduced an alternative wound local treatment, already used in 2012 in the Democratic Republic of Congo to treat the Buruli Ulcer [5,6], named Hyperoil®, a hypericum flowers (Hypericum perforatum) extract in neem oil (Azadirachta indica) produced by RIMOS srl Mirandola (MO) – Italy: it was the only available antiseptic. It was available in oily, gel and medicated gauzes formulation (Medical Device Class IIB CE0476), and it has already been used in complicated diabetic foot ulcers [7].

## Case Presentation

18 months old female with complicated SAM (WHO Z-score < -3), attended the NRC. The local assistant (Sister Emilienne) rated her overall clinical status as a very critical, with high death risk because of extended, exudating, smelling, advanced (2 months) edema and infected lesions on both lower legs.

To contrast F's severe conditions, the standard hyperproteic feeding treatment (multivitamin, nistatine, amoxicilline) as promoted by the WHO guidelines [8] was immediately started leading to the clinical recovery of F in 4 weeks.

Lower legs lesions were cleaned with ozonated water [9,10] by Sister Emilienne and treated with Hyperoil® medicated gauzes, kindly




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**Figure 1:** Before the first application of Hyperoil® medicated gauze.
Wounds in the legs have edema, exudate secretion and perilesional skin inflammation.
The wound in the left leg has fibrin.
The wound in the right leg has extended skin discoloration.

donated by Helios Med Onlus.

Sister Emilienne observed an unexpected improvement of lesions (Figure 1) 2 days after the first dressing. More in detail, she reported reduced fibrin (Figure 2A), edema, inflammation and exudate secretion, perilesional skin recovery (Figure 2B), smell disappearance and cleaned wound bed.

The child continuously improved her general health status during the first week she underwent the best clinical treatment as well as the lower legs lesions. She reached the complete wounds recovery in 3 weeks, without any local skin discoloration.

Sister Emilienne, having a vast experience in children with SAM, was really surprised of this outcome because of the critical health conditions of the patient.

## Management

The lower limb ulcer bed cleansed with ozonated water, the ulcers were treated with Hyperoil® medicated gauzes applied (Figure 1) every day for the first week and every three days until complete healing. The change of the dressing was atraumatic.

The perilisional area was carefully cleaned with normal Ringer solution and gauze with a few drops of Hyperoil® oil. The ulcer bed and edges were cleaned from exudates and fibrin residuals as well as the necrotic materials were removed with a gauze soaked with Hyperoil® oil.

In addition, to avoid infection, the ulcers were covered with gauze bandage to protect the ulcer from dust and dirt and to maintain the dressing in the appropriate zone.

Surprisingly, 2 days after the first application with Hyperoil® medicated gauzes, ulcer bed, edges, skin hypochromia were reduced with improvement of surrounding skin trophism (Figure 2B). Also the wound bed in the left leg showed an improvement in the same time with a reduction of fibrin (Figure 2A).

The ulcers were completely cleaned after the first week of therapy showing a partial re-epithelialization in two weeks without secondary infection, and the complete healing in three weeks in both legs.

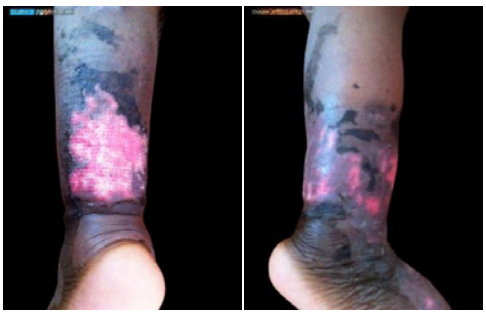

**Figure 2:** Two days after the first application of Hyperoil® medicated gauze.
The wounds in the legs show reduced edema, inflammation and exudate secretion.
A. The wound in the left leg has a cleaned bed with almost complete fibrin disappearance.
B. The wound in the right leg has improved the wound bed and perilesional skin with recovery local skin coloration.

## Discussion

Hyperoil® medicated gauzes proved to be a new therapeutic approach for the local treatment of ulcers in children with severe malnutrition, especially in areas with limited resources. Indeed, mother's residential and household feeding characteristics appear to influence children's nutritional status. In Benin, in fact, acute malnutrition remains an important killer of children under five years of age. The under-5 mortality rate was around 90 deaths per 1,000 live births in 2012 while the infant mortality rate was 59 [11]. However, Benin still has a long way to go to achieve the Millennium Development Goal of eradicating extreme poverty and hunger.

FAOSTAT [12] highlighted a decreasing percentage of children under 5 years of age who are underweight moving from 26.8% in 1996 to 18.0% in 2014. Also the prevalence of undernourishment (3 years average) declined from around 28.0% in the mid-90s to less than 10.0% in 2013. More in detail, at the time of this case report, the underweight prevalence in children under 5 in rural areas was 22.5%, but the percentage of severe acute malnutrition in children under 5 was 7.5% [8]. In fact, malnourished children from 6 months up to 7 years attend the NRC because their mothers are not able to feed them, due to local food taboos and/or to a new pregnancy that made mothers stop breastfeeding.

In isolated areas like Wawata-Zounto, Sèdjè, Kpatchame that are the villages served by the NRC in Zinviè, blood and urine tests used to measure the patient's levels of vitamins, minerals, and waste products were not available and also clinical nutritionist or dietician were not there to confirm the presence of malnutrition. Thus, diagnosis had to be performed on Body Mass Index (BMI) according to WHO standards [1] and measuring the circumference of the upper arm.

Malnutrition has a skin manifestation as a consequence of kwashiorkor and marasmus.

Especially in the case of kwashiorkor, alimentation based on carbohydrates determines an increase in insulin production with a consequent reduction in protein synthesis. Previous studies [13] showed that in kwashiorkor collagen maturation is altered and that some amino acids in skin are lower than usual (in particular glycine). Cutaneous lesions in this condition begin with dark patches on

juncture surfaces especially on ankles, knees, elbows and wrists. Then, lesions become desquamating with skin loss and tend to spread also in other body areas [3]. In particular, the granulosum and spinosum layers are involved and characterized by strong atrophy.

Heliskov et al. suggested a classification for cutaneous changes in SAM [14]. They identified 5 signs (telogenic effluvium, pigmentary changes, ichthyosiform skin changes, lichenoid skin changes and various stages of bullae-erosions-desquamation) that can exist in both edematous and non edematous forms of SAM. These signs should be considered as a valid parameter to evaluate lesion severity and to choose the right medical approach.

Lesions usually recover after a correct diet assessment but they still represent a loss in skin barrier capacity, making infection easier to set in and retarding patient healing.

According to WHO indications, lesions have to be treated applying paraffin gauzes and antimycotic creams for almost two weeks and zinc or castor oil treatment after 1% potassium permanganate bath. To avoid skin and, consequently, systemic infection, lesions should be sterilized and patient needs to receive systemic antibiotic therapy [8].

Having a cheap and simple-to-be-transported therapeutic option as Hyperoil® to treat patients with ulcers due to SAM, could give to trained health care providers a new topical treatment. This approach to children with SAM ulcers, including nutritional education, could permit in allows SAM ulcers treatment and control.

## Conclusion

The surprising outcome observed in the treatment of lower legs lesions due to SAM with Hyperoil® suggests its use as a new possible local therapeutic option to reduce the risk of secondary infection due to ulcers and to avoid systemic antibiotic therapy.

## Acknowledgment

The authors are thankful to the Filles de Saint Camille for their hospitality in Zinviè.

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CASE REPORT

# The use of an extract of *Hypericum perforatum* and *Azadirachta indica* in advanced diabetic foot: an unexpected outcome

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## SUMMARY

This is the first case reporting the results of using an extract of *Hypericum* flowers (*Hypericum perforatum*) and neem oil (*Azadirachta indica*) in foot wounds with exposed bone in a patient with bilateral advanced diabetic ulcers. The effective use of this cheap treatment in patients with diabetic lesions on the feet, if confirmed in a wide controlled study, might allow the caregivers to take care of patients at home.

## BACKGROUND

Diabetes and its complications are becoming one of the major concerns for healthcare systems.[1]

As diabetic patients with lower extremity ulcers have a poorer clinical outcome and more difficult management, the home care of diabetic ulcers should allow a significant improvement in the management of diabetic complications.[2]

## CASE PRESENTATION

A man aged 72, with type 2 diabetes from 40 years, came to our angiological centre on 6 April 2011 with diabetic feet ulcers in both legs.

An ischaemic cutaneous lesion was observed on the right foot, at the top of the big toe, as a small ischaemic skin deficit (less than 0.5 cm large) (figure 1A).

The patient declared that he had had a myocardial infarct in March 1997, followed by aortocoronary bypass in June 1999; he had a cardiac pacemaker implanted, since February 2007, for ischaemic dilated cardiomyopathy (ejection fraction (EF), 20%).

The patient was treated with statins (simvastatin 20 mg/die), diuretics (furosemide 25 mg/die and canrenone 50 mg/die), antihypertensives (carvedilol 12.5 mg/die and irbesartan 150 mg/die), cardiac glycosides (metildigoxin 0.1 mg/die), antiaggregant (ticlopidine hydrochloride 500 mg/die) and insulin. As the heart surgery procedure was performed in a different hospital, no further details about the patient's intrasurgical therapies are available to the author.

On 2 April 2011, when the last control was performed, glycated haemoglobin A1c (HbA1c) was 13.2%, fasting glycaemia was 166 mg/dl, and therapy for diabetes was 12 IU of rapid acting insulin three times a day and 10 IU of basal insulin at bedtime.

The patient was able to walk with claudicatio intermittens.

## INVESTIGATIONS

During the assessment visit on 6 April 2011, echocolor Doppler showed a sub-genicolate arteriopathy to both the feet, which resulted more serious on the left foot from supine/depend transcutaneous oxygen and carbon dioxide partial pressure, performed according to Melillo *et al*[3]. Nevertheless, this exam highlighted microvascular parameters indicating a good metabolic compensation of the tissue on both the legs (table 1).

In August 2011, anticoagulant therapy with warfarin (2 mg/die) was started because of cardiac uncompensation owing to the previously described cardiomyopathy and the presence of left cardiac intraventricular thrombosis. Microvascular parameters worsened at the right foot and were stable at the left foot (table 1); glycaemic control was rapidly improving (HbA1c=8.0%). In November 2011, a pacemaker was substituted because of various cardiac uncompensation episodes (EF: 20%). On 27 December 2011, the cutaneous metabolic parameters at the left foot showed supine hypoxia with tissue acidosis and positive postural recovery, whereas the tissue metabolic measurements were relatively stable at the right foot (table 1).

At the same time, glycaemic control was stable from previous control (HbA1c=7.6%) and anticoagulant therapy was stable and well monitored.

### Right foot

The little ischaemic lesion at the right foot worsened dramatically in the next month, and a cyanotic tissue area was observed on 14 July 2011 (figure 1B). Therefore, a first amputation of the two distal phalanges of the big toe was needed. As the tissue was vital, the remaining part of the foot was covered using homologue tissue. Five days after amputation of the big toe, an extension of the lesion was observed, and thus, another intervention removing the distal part of the first metatarsal bone was performed. The necrosis continued to enlarge until the exposition of the first metatarsal bone occurred on 30 August 2011 (figure 1C). Because of this, all the metatarsal bones were removed in another surgical procedure which was carried out in September 2011, followed by further bone remodelling on 15 December 2011.

In February 2012, another surgical toilet was needed, with the implantation of homologue epidermal tissue, because of ulcer worsening.

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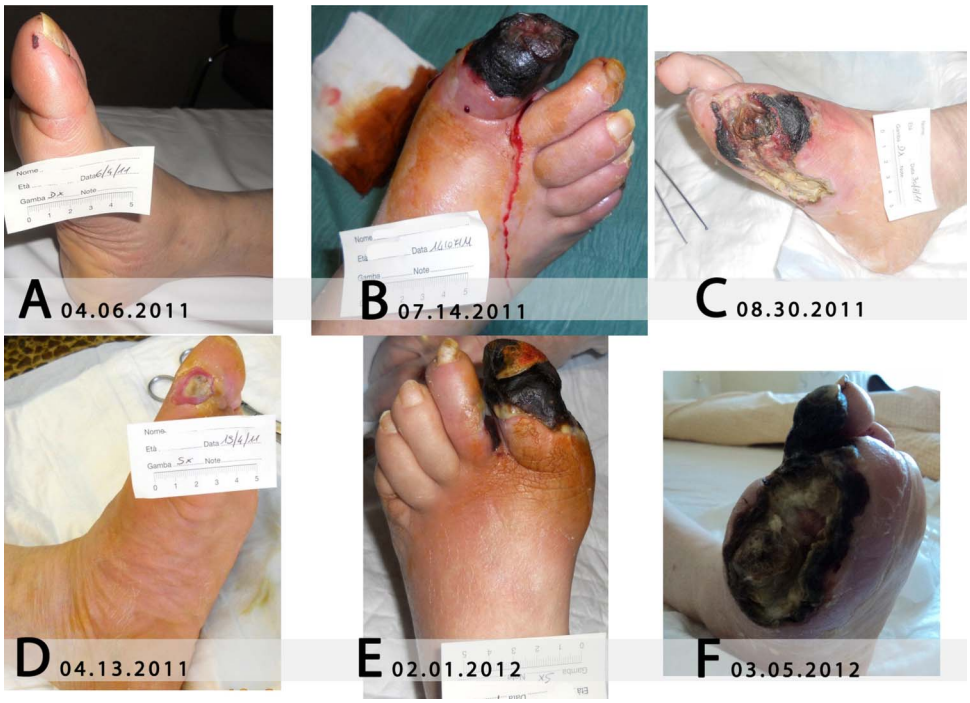


**Figure 1** Ulcers evolved at the right foot (A–C) and the left foot (D–F) before the use of Holoil.

### Left foot

A worsening chronic skin ulcer on the left big toe (referred as appeared since 1 year in April 2010) had skin graft transplantation with homologue tissue, performed in our structure, on 7 April 2011. This was documented by a photo on 13 April 2011 (figure 1D), when it was about 1 cm large and 0.5 cm deep, with an exposed interphalanx ligament, even though the surgical procedure was performed a few days before.

The ulcer at the big toe of the left foot had initial previous treatment with a mixture of clostridiopeptidase and cloramfenicole (Iruxol 30G),[4] applied daily in a different structure; the lesion continuously worsened until ligament exposure.

On 15 December 2011, another surgical toilet, with skin graft transplantation, was performed. In the next month, a wide acral sclerosis of the big toe, similar to the one observed a few months before at the right foot, occurred, which then extended to the second finger (figure 1E). The cause of this sclerosis was supposed to be a distal thrombosis, as documented by cutaneous metabolic parameters collected on 27 December 2011.

On 1 February 2012, both the first and second fingers of the left foot were cut and another transplantation of homologue tissue was performed. After this intervention, the necrosis extended to the third finger and to the amputation borders; the lesion was treated with patches of silver hydrofiber to reduce oedema and the possibility of having an infection. However, at this time, the microvascular parameters evaluation (table 1) showed a relatively stable cutaneous tissue oximetry and capnometry.

**Table 1** Microvascular parameters with supine/depend foot; trends through

| Date | Left foot (mm Hg [$O_2$]) | Left foot (mm Hg [$CO_2$]) | Right foot (mm Hg [$O_2$]) | Right foot (mm Hg [$CO_2$]) |
|---|---|---|---|---|
| 6 April 2011 | 48/53 | 37/36 | 50/60 | 37/35 |
| 3 August 2011 | 46/52 | 37/36 | 34/46 | 40/36 |
| 27 December 2011 | 34/43 | 40/36 | 51/63 | 37/35 |
| 1 February 2012 | 38/44 | 37/36 | 51/63 | 37/35 |
| 28 July 2012 | 45/53 | 37/36 | 49/59 | 37/35 |

### Both feet

On 5 March 2012, gangrene had affected the third left finger, and the cutaneous border necrosis exposed the first residual metatarsal of the big toe (figure 1F).

The lesion at the right foot showed adhered fibrin with hyperkeratotic borders and clear bone exposition on 13 March 2012 (figure 2A); these abnormalities indicate that the lesion clearly did not proceed to recovery.

Thus, another surgical debridement and cutaneous transplantation of both lesions could be needed.

## TREATMENT

Because of transportation difficulties of the patient, the relatives and the medical staff agreed to begin the use of Holoil gel to treat the left foot ulcer on 5 March 2012 and Holoil-garze for the right foot ulcer on 13 March 2012, instead of other surgical skin graft reimplantations.

Holoil gel is a mixture of *Hypericum* flower extract (*Hypericum perforatum*) and neem oil (*Azadirachta indica*) produced by RIMOS S.R.L. Mirandola (MO)—Italy (Medical Device Class IIB CE0476). The efficacy of this treatment on an ulcerated vascular leg was described in a previous report.[5]

The patient's relatives were instructed to clean the lesions with Holoil two times a week and to perform an appropriate bandage to protect the lesion from infections and dust.

## OUTCOME AND FOLLOW-UP

In the next 4 months, the ulcers at both the feet continuously improved.

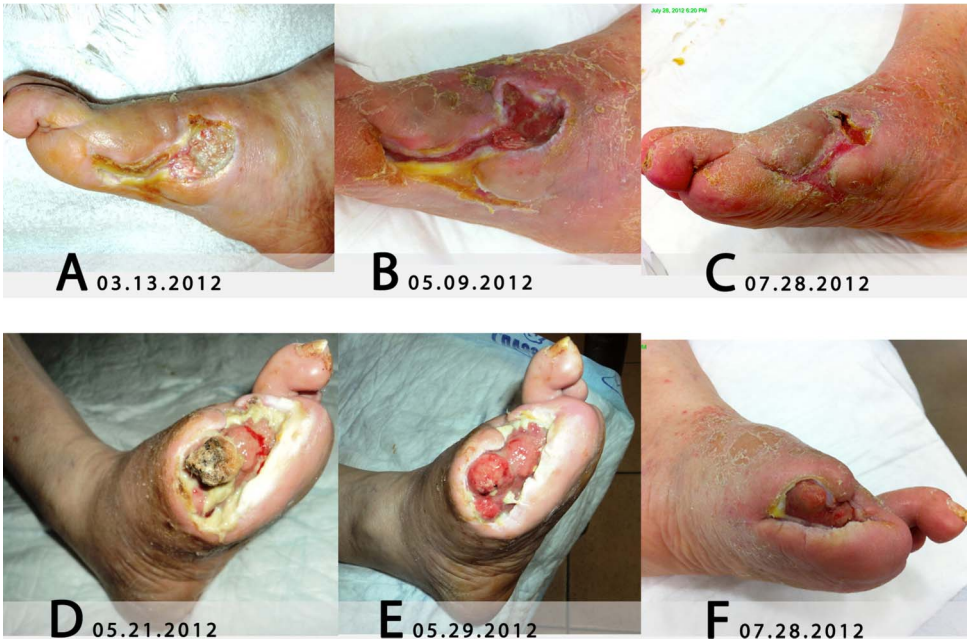


**Figure 2** Ulcers evolved before Holoil treatment on the right foot (A), and after starting the use of Holoil at the right foot (B and C) and the left foot (D–F).

The right foot ulcer showed granulation tissue and wound healing epithelisation and reduced in size (figure 2B, C).

The left foot ulcer reduced in size and the granulation tissue continuously enlarged (figure 2D). The periosteal was reformed at the exposed metatarsal bone (figure 2E) and a continuous reformation of the cutaneous tissue on the lesion was observed (figure 2F).

During this period of the home wound care, the patient received a cleaning of the lesions with Holoil, only two times a week, performed by relatives without any other surgical or clinical intervention. There were no changes in any other treatment of the patient or significant improvements in glycaemic control (HbA1c was constantly between 7.6% and 7.7%) or clinically relevant changes observed in microvascular parameters (table 1).

## DISCUSSION

The use of *H perforatum* on depressed patients is well known and described.[6] *H perforatum* was also proposed as an anticancer drug that induces apoptosis in tumour cells[7 8] and inhibits metastasis in vivo.[9] An inhibitory effect of hyperforin on the neovascularisation of an experimental murine tumour model has also been suggested,[4] as the in vivo inhibition of angiogenesis and the in vitro inhibition of several key steps of angiogenesis, including endothelial cell proliferation, differentiation and invasion, as well as an extracellular matrix degradation by matrix metalloproteinase-2 and urokinase.[10]

The anti-inflammatory effects of *H perforatum* extracts were recently demonstrated,[11] thus providing the rationale for using these extracts in lower leg wounds, together with neem oil extract.[12]

Neem extracts have been used for centuries in traditional Indian medicine; its oil, obtained with cold extraction from its berries, is also included in the Ayurvedic Pharmacopoeia of India.[13] Neem oil has shown to have cicatrising,[14] bacteriostatic[15] and anti-inflammatory properties. Its anti-inflammatory activity seems to be due to the presence of a limonoid (epoxyazadiradione) showing its effects on several inflammation markers of the macrophage migration inhibitory factors family.[16]

Holoil is a mixture of *Hypericum* and neem extracts: its original formulation could explain the observed effects of fibrin reduction and the improvement of granulation and cutaneous tissue. This is the first case where the positive use of Holoil, together with improved diabetes control, has clearly reversed the worsening of diabetic foot ulcers in a patient having severe diabetic and cardiovascular diseases. The use of Holoil was started when the patient had significantly improved his glycaemic control, and thus, we cannot evaluate if this improvement was due to the patient's improved glycaemic control or this medication or both. For sure, the patient's management had improved when the use of Holoil was started by his caregivers (relatives) at their home, thus avoiding the patient's travels to the hospital for continuously needed surgical toilets of the ulcers. Furthermore, the use of Holoil could have reduced the possibility of local reinfection, supporting the maintenance of diabetes control, as recurrent infections contribute to uncontrolled diabetes.

### Learning points

- As both the feet showed an improvement in ulcer lesions when cleaning with Holoil was started, we will have to start its use earlier to understand how and when the use of Holoil could have reduced the worsening of diabetic feet ulcers.
- For future patients attending our angiological centre, we suggest patients start using Holoil at home, as a starting treatment for diabetic foot lesions, so they better understand how its use can improve wound healing and thus improve their outcome.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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BMJ Case Reports

# The use of an extract of Hypericum perforatum and Azadirachta indica in advanced diabetic foot: an unexpected outcome.


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|---|---|
| Journal: | *BMJ Case Reports* |
| Manuscript ID: | bcr-2012-007299.R5 |
| Manuscript Type: | Unexpected outcome (positive or negative) including adverse drug reactions |
| Date Submitted by the Author: | 20-Dec-2012 |
| Complete List of Authors: | Iabichella, Maria Letizia; Barbantini Clinic , Angiology |
| Keywords: | Complementary medicine 47, Dermatology 57, Drug therapy related to surgery 1321 < Drugs and medicines, Diabetes 77 < Endocrinology 1325, Healthcare improvement and patient safety 1492 |
| | |

## TITLE OF CASE

The use of an extract of Hypericum perforatum and Azadirachta indica in advanced diabetic foot: an unexpected outcome.

## AUTHORS OF CASE

Maria Letizia Iabichella

## SUMMARY

This is the first case reporting the results of using an extract of hypericum flowers (Hypericum perforatum) and nimh oil (Azadirachta indica), in foot wounds with exposed bone in a patient with bilateral advanced diabetic ulcers.

The effective use of this cheap treatment in patients with diabetic lesions on feet, if confirmed in a wide controlled study, might allow the caregivers care of patients at home.

## BACKGROUND

Diabetes and its complications are becoming one of the major concerns for healthcare systems[1].

As diabetic patients with lower extremity ulcers have poorer clinical outcome and more difficult management, the home care of diabetic ulcers should allow a significant improvement in the management of diabetic complications[2].

## CASE PRESENTATION

A men aged 72, with type 2 diabetes from 40 years met our angiological center on 6-April-2011 with diabetic feet ulcers at both legs.

An ischemic cutaneous lesion was observed on the right foot at the top of the big toe, as a small ischemic skin deficit (less than 0.5 cm large) (Fig. 1 A).

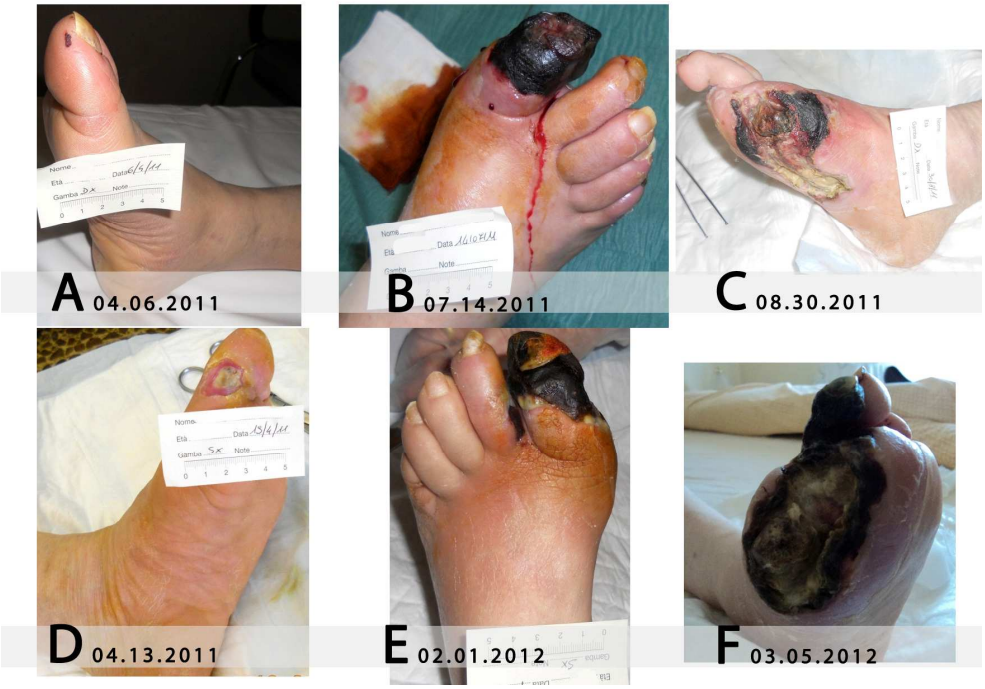


Fig. 1: Ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) before the use of Holoil.

The patient declared he had a myocardial infarct on March 1997, followed by aorto-choronaric bypass on June 1999; he has implanted Cardiac Pace-Maker, since February 2007, for ischemic dilated cardiomyopathy (Ejection Fraction, EF 20%).

The patient was treated with statins (simvastatine 20 mg/die) diuretics (furosemide 25 mg/die and canrenon 50 mg/die), antihypertensives (carvedilol 12,5 mg/die and irbesartan 150 mg/die), cardiac glycosides (metildigoxin 0.1 mg/die), antiaggregant (ticlopidine hydrochloride 500 mg/die) and insulin. As the heart surgery procedure was performed in a different hospital, no further details about patient's intra-surgical therapies are available to the author.

On 2-April-2011, when the last control was performed, HbA1c was 13.2%, fasting glycaemia 166 mg/dl, and therapy for diabetes was 12 IU of rapid acting insulin 3 times a day and 10 IU of basal insulin at bedtime.

The patient was able to walk with claudicatio-intermittens.

**INVESTIGATIONS**

During the assessment visit on 6-April-2011, echo-color-Doppler showed a sub-genicolate arteriopathy to both feet which resulted more serious on the left foot from supine/depend trans-cutaneal oxygen and carbon dioxide partial pressure, performed according with Melillo et al.[3]. Nevertheless, this exam highlighted microvascular parameters indicating a good metabolic compensation of the tissue on both legs (Tab. 1).

On August 2011 anticouagulant therapy with warfarin (2 mg/die) was started because of cardiac uncompensation due to the previously described cadiomiopathy and the presence of left cardiac intraventricolar thrombosis. Microvascular parameters worsened at the right foot, and were stable at the left foot (Tab. 1); glycaemic control was rapidly improving (HbA1c = 8.0%).

On November 2011, pace maker was substituted because of various cardiac uncompensation episodes (EF: 20%). On 27-December-2011, the cutaneous metabolic parameters at the left foot showed supine hypoxia with tissue acidosis and positive postural recovery, while the tissue metabolic measurement were relatively stable at the right foot (Tab. 1).

At the same time, glycaemic control was stable from previous control (HbA1c = 7.6%) and anticoagulant therapy was stable and well monitored.

Right foot

The little ischemic lesion at the right foot worsened dramatically in the next months, and a cyanotic tissue area was observed on 14-July-2011 (Fig. 1 B). Therefore, a first amputation of the two distal phalanges of the big toe was needed. As the tissue was vital, the remaining part of the foot was covered using homologue tissue. Five days after big toe amputation, an extension of the lesion was observed and, thus, a further intervention removing the distal part of the first metatarsal bone was performed. The necrosis continued to enlarge until the exposition of the first metatarsal bone, occurred on 30-August-2011 (Fig. 1 C). Because of this, all the metatarsal bone was removed in a further surgical procedure occurred on September 2011, followed by a further bone remodelling on 15-December-2011.

On February 2012 another surgical toilette was needed, with the implantation of homologue

epidermal tissue, because of ulcer worsening.

Left foot

A worsening chronic skin ulcer on the left big toe (referred as appeared since 1 year on April 2010) had skin graft transplantation with homologue tissue, performed in our structure, on 7-April-2011. This was documented by photo on 13-April-2011 (Fig. 1 D), only, when it was about 1 cm large and 0.5 cm deep, with exposed inter-phalanx ligament, even after the surgical procedure performed a few days before.

The ulcer at big toe of the left foot had initial previous treatment with a mixture of clostridiopeptidase and cloramfenicole (Iruxol 30G)[5], applied daily in a different structure; the lesion continuously worsened until ligament exposure.

On 15-December-2011, a further surgical toilet, with skin graft transplantation, was performed. In the next month, a wide acral sclerosis of the big toe, similar to the one observed a few months before at the right foot, occurred and, then, it extended to the second finger (Fig. 1 E). The cause of this sclerosis was supposed to be a distal thrombosis, as documented by cutaneous metabolic parameters collected on 27-December-2011.

On 1-February-2012 both first and second fingers of the left foot were cut and further transplantation of homologue tissue was performed. After this intervention, the necrosis extended to the third finger and to the amputation borders; the lesion was treated with patches of silver hydrofiber to reduce oedema and the possibility of having an infection. However, at this time, the microvascular parameters evaluation (Tab. 1) showed a relatively stable cutaneous tissue oximetry and capnometry.

Both feet.

On 5-March-2012 gangrene is at the third left finger and the cutaneous border are necrosis with exposed the first residual metatarsal of the big toe (Fig. 1 F).

The lesion at the right foot showed adhered fibrin with hyperkeratotic borders and clear bone

exposition on 13-March-2012 (Fig. 2 A); these abnormalities indicate that the lesion clearly did not proceed to recovery.

Thus, another surgical debridement and cutaneous transplantation to both lesions could be needed.

**DIFFERENTIAL DIAGNOSIS**

**TREATMENT**

Because of transportation difficulties of the patient, the relatives and the medical staff agreed to begin the use of Holoil gel to treat the left foot ulcer on 5-March-2012, and Holoil-garze for right foot ulcer on 13-March-2012, instead of further surgical skin graft re-implantations.

Holoil gel is a mixture of hypericum flowers extract (Hypericum perforatum) and nimh oil (Azadirachta indica) produced by RIMOS S.r.L. Mirandola (MO) - Italy (Medical Device Class IIB CE0476). The efficacy of this treatment on ulcer vascular leg was described in a previous report[4].

Patient's relatives were instructed to clean lesions with Holoil two times a week and to perform an appropriate bandage to protect the lesion from infections and dust.

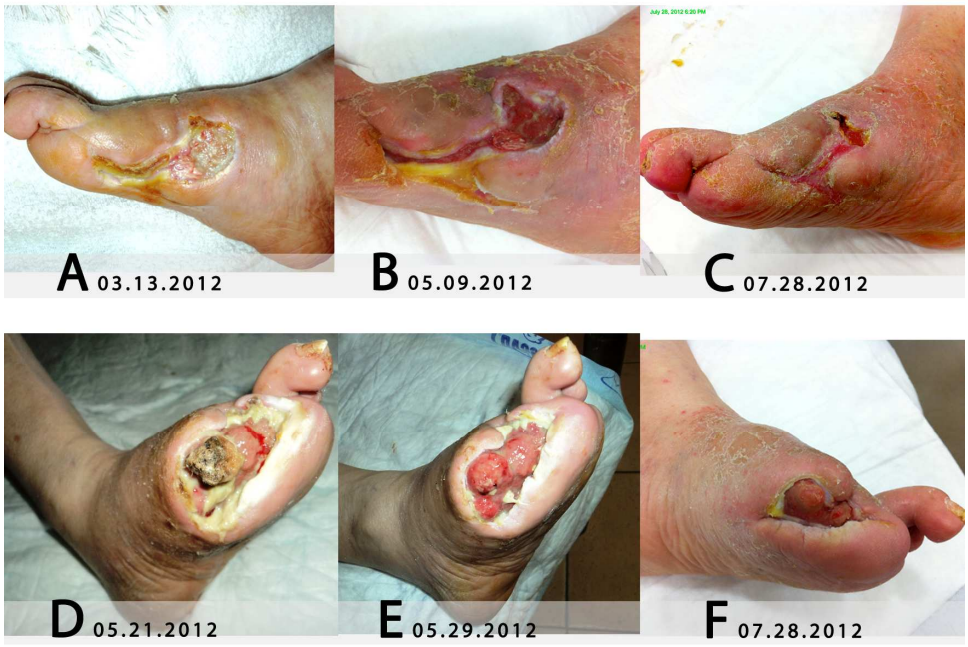


Fig. 2: Ulcers evolutions before Holoil treatment on right foot (A), and after starting the use of Holoil at the right foot (B, C) and the left foot (D, E, F)

**OUTCOME AND FOLLOW-UP**

In the next 4 months, the ulcers at both feet continuously improved.

The right foot ulcer showed granulation tissue, wound healing epithelisation, and reduced its size (Fig. 2 B, 2 C).

The left foot ulcer reduced its size, the granulation tissue continuously enlarged (Fig. 2 D), the periosteal was re-formed at the exposed metatarsal bone (Fig. 2 E) and a continuous reformation of the cutaneous tissue on the lesion was observed (Fig. 2 F).

During this period of the home wound care, the patient received only a 2 times a week cleaning of the lesions Holoil, performed by relatives without any other surgical or clinical intervention and there were neither changes in any other treatment of the patient nor were significant improvements in glycaemic control (HbA1c was constantly between 7.6% and 7.7%), nor clinically relevant changes were observed in microvascular parameters (Tab. 1).

Table 1. Microvascular parameters with supine/depend foot; trends through time.

| Date | Left foot (mmHg [$O_2$]) | Left foot (mmHg [$CO_2$]) | Right foot (mmHg [$O_2$]) | Right foot (mmHg [$CO_2$]) |
|---|---|---|---|---|
| 6-April- 2011 | 48/53 | 37/36 | 50/60 | 37/35 |
| 3-August-2011 | 46/52 | 37/36 | 34/46 | 40/36 |
| 27-December-2011 | 34/43 | 40/36 | 51/63 | 37/35 |
| 1-February-2012 | 38/44 | 37/36 | 51/63 | 37/35 |
| 28-July-2012 | 45/53 | 37/36 | 49/59 | 37/35 |

## DISCUSSION

The use of Hypericum perforatum on depressed patients is well known and described[6]. Hypericum perforatum was also proposed as anticancer drug that induces apoptosis in tumor cells[7,8] and inhibits metastasis in vivo[9]. An inhibitory effect of hyperforin on the neo-vascularization of an experimental murine tumour model has also been suggested[5], as the in-vivo inhibition of angiogenesis and the in-vitro inhibition of several key steps of angiogenesis, including endothelial cell proliferation, differentiation and invasion, as well as extracellular matrix degradation by MMP-2 and urokinase[10].

The anti-inflammatory effects of Hypericum perforatum extracts were recently demonstrated[11] thus providing the rationale for using these extracts in lower legs wounds, together with nimh oil extract[12].

Nimh extracts have been used for centuries in the traditional Indian medicine; its oil, obtained with cold extraction from its berries, is also included in the Ayurvedic Pharmacopoeia of India[13]. Nimh oil has shown cicatrizing[14], bacteriostatic[15], anti-inflammatory properties. Nimh oil anti-inflammatory activity seems to be due to the presence of a limonoid (epoxyazadiradione) showing effects on several inflammation markers of the macrophage migration inhibitory factors family[16]. Holoil is a mixture of hypericun and nimh extracts: its original formulation could explain the

observed effects on fibrin reduction and the improvement of granulation and cutaneous tissue. This is the first case where the positive use of Holoil, together with improved diabetes control, has clearly reversed the worsening of diabetic foot ulcers in a patient having severe diabetic and cardiovascular diseases. The use of Holoil was started when the patient had significantly improved his glycemic control and, thus, we cannot evaluate if this improvement was due to patient's improved glycaemic control or by this medication or both. For sure, patient's management improved when the use of Holoil was started as Holoil was used by caregivers (relatives) at their home, thus avoiding patient's travels to hospital for continuously needed surgical toilets of the ulcers. Furthermore, the use of Holoil could have reduced the possibility of local reinfection, supporting the maintenance of diabetes control, as recurrent infections contribute to uncontrolled diabetes.

**LEARNING POINTS/TAKE HOME MESSAGES**

- As both feet showed an improvement in ulcer lesions when cleaning with Holoil was started, we will have to start its use earlier to understand how and when the use of Holoil could have reduced the worsening of diabetic feet ulcers.
- In next patients attending our angiological center we'll suggest patients to start using Holoil at home, as a starting treatment for diabetic foot lesions, to better understand how its use could improve wound healing and, thus, improve patient's outcome.

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**Figure captions**

Fig. 1: Ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) before the use of Holoil.

Fig. 2: Ulcers evolutions before Holoil treatment on right foot (A), and after starting the use of Holoil at the right foot (B, C) and the left foot (D, E, F).



**Date: 20-December-2012**

**TITLE OF CASE**

The use of an extract of Hypericum perforatum and Azadirachta indica in advanced diabetic foot: an unexpected outcome.

**AUTHORS OF CASE**

Maria Letizia Iabichella

**DESCRIPTION**

Figure 1 describes foot ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) before the use of Holoil. Figure 2 show Ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) after starting the use of Holoil.

This is the first case where the positive use of Holoil has clearly reversed the worsening of diabetic foot ulcers in a patient having severe diabetic and cardiovascular diseases. The use of Holoil improved patient's management, too, as Holoil was used by caregivers (relatives) at their home, thus avoiding patient's travels to hospital for continuously needed surgical toilets of the ulcers.

As both feet showed an improvement in ulcer lesions when cleaning with Holoil was started, we will have to start its use earlier to understand how and when the use of Holoil could have reduced the worsening of diabetic feet ulcers. In next patients attending our angiological center we'll suggest patients to start using Holoil at home, as a starting treatment for diabetic foot lesions, to better understand how its use could improve wound healing and, thus, improve patient's outcome.

**REFERENCES**

**Figure captions**

Fig. 1: Ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) before the use of Holoil.

Fig. 2: Ulcers evolutions at the right foot (A, B, C) and the left foot (D, E, F) after starting the

use of Holoil.

**Copyright Statement**



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