POSITION DOCUMENT

ITALIAN WOUND CARE ASSOCIATION
(ASSOCIAZIONE ITALIANA ULCERE CUTANEE - AIUC)

ISCHEMIC ULCER AND CRITICAL ISCHEMIA

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Ischemic ulcer and critical ischemia

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PRESENTATION

This is a choral chant on an issue which has been well identified as the third evolitional stage of chronic obstructive arteriopathy, which has still to be planned as a stand alone signal and symptom. The debate is still open on whether a consequence of several and different vascular and non vascular diseases, could have, in therapeutic response, a common denominator or if the various causes represent the right way to arrive at a proper approach of the consequences. This is not a simple problem to be underestimated given that the whole History of Medicine throughout centuries, since the Priestly Medicine of the Egyptians, has always revolved around this dilemma: whether it is a holistic concept in a therapeutic sense or a “reductive” one of cause and effect. Not really like “the egg or the hen” because in this specific case all the eggs are equal but the hen changes although it apparently keeps laying the same eggs. So congratulations to the Authors and particularly to my friend Giorgio Guarnera for his umpteenth attempt to combine, with courage, a sign and so the Scientific Association to which he belongs, with the several causes constituting it.

They are definitely not a re-copy of the useful but boring Guidelines, but rather a personal flair founded on Medicine Based on Experience; it was about time to solidify into a personal object something which, while respecting the norms of Evidence, would produce something on which to reflect and work.

This is not insignificant, because this position document should be read with constructive criticism while thinking that the apparent contrast with official science, is not the product of a lack of awareness but a careful reflection which our French colleagues have never abandoned: “il faut reflechir” is a dictum appearing nearly very slavishly in the science programs of our Colleagues from the other side of the Alps.

And so here it is, an innovative and brave document, which has been both difficult and bold to compile.

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DEFINITION OF CRITICAL ISCHEMIA

The definition of critical lower limb ischemia (CLLI) indicates the clinical picture characterized by rest pain and/or trophic lesions of different degrees and extents (see the Lériche-Fontaine and Rutherford classifications reported in Table I) such as ulcers and/or gangrene, having arisen over 15 days prior, secondary to arteriopathy with an obliterative evolution, and in hemodynamic terms, from systolic pressure measurements <50 mmHg at the ankle and <30 mmHg at the big toe. Under the microcirculatory profile, it is characterized by the regional reduction of the transcutaneous oxygen tension (<30 mmHg) at the affected forefoot.

The diagnosis of critical ischemia must be suspected in the presence of the following signs or symptoms:

— rest pain in the lower limbs, mainly at night or when supine (Lériche-Fontaine stage III or Rutherford degree II, cat. 4) that lasts more than 15 days and requires analgesic treatment;
— acral focal skin lesions (Lériche-Fontaine stage IV or Rutherford degree III, cat. 5);
— extensive skin lesions or gangrene (Lériche-Fontaine stage IV or Rutherford degree III, cat. 6)

Many experts believe that the finding of severe claudication, intending, with this adjective, a range of free movement of a few steps, should also be added to this “official” classification.

This definition joins different clinical stages that correlate to a high risk of amputation and death, criticalities that also characterize the finding of severe claudication. The incidence of critical limb ischemia in Europe is approximately 450 cases/million inhabitants with a relative risk of amputation of 50% in non-revascularized patients and 26% in patients subjected to direct or indirect revascularization treatments, while the relative risk of death is 50% and 18%, respectively. As known, radical limb surgeries are burdened by a very poor prognosis; about 30% of the patients die within the subsequent 12 months, while another 30% achieve partial self-sufficiency and only the remaining 30% reach a condition of total autonomy and self-sufficiency. However, a notable difficulty remains in the study of populations with CLLI in consideration of the notable number of patients lost during the various follow-ups or deceased during longitudinal studies, resulting, unfor-

| Table I.—Clinical staging of chronic obliterative arteriopathy of the lower limbs according to Lériche-Fontaine and according to Rutherford. |
|---|---|---|
| - Lériche-Fontaine classification | | |
| Stage | Symptomatology | Clinical examination |
| I | Asymptomatic | |
| II | Intermittent claudication | Manifestation of skin and skin adnexa dystrophy |
| III | Rest pain | Pallor - cyanosis |
| IV | Trophic lesions | Focal ulcers - gangrene |
| - Rutherford classification | | Clinical |
| Degree | Category | |
| 0 | Asymptomatic | |
| I | 1 | Mild claudication |
| I | 2 | Moderate claudication |
| I | 3 | Severe claudication |
| II | 4 | Rest pain |
| III | 5 | Minor tissue lesions |
| III | 6 | Major tissue lesions |

The two classifications substantially correspond. To better identify the claudication and monitor any improvement, Rutherford’s classification applies three categories; for similar reasons, in the course of time, Lériche’s original stage II has been classified into IIA and IIB in relation to the seriousness of the symptom.
A sufficiently homogeneous datum is the increase in the incidence of this nosological finding after sixty years of age.

**Epidemiology of ischemic ulcer**

The ischemic ulcer is set in the nosological context of a critical limb ischemia.

On the score of evaluations based on the percentages of major amputations for atherosclerotic lesions, it could be affirmed that the annual incidence of critical limb ischemia is between 500 and 1000 new cases every year per million population.\(^1\)

It is perhaps still more difficult to obtain definite data on the prevalence of ischemic ulcers. There exist significant differences between several studies, linked to a series of factors: 1) studies of global or actual prevalence (should all ulcers so be considered or only active ones?); 2) the specialist branch to which the concerned clinician belongs; 3) inclusion and exclusion criteria (some studies only consider leg ulcers but not foot ulcers); 4) age of the population sample (there is a clear association between age and some types of chronic ulcers); 5) methodology of the study (a questionnaire offered directly to the population can lead to a high percentage of false positives).\(^2\) To all these factors, presenting a potential major limit to the epidemiological investigations on all types of skin ulcers, it is essential in ischemic ulcers to consider the gangrenous ulcer as separate.

Generally, it has been presumed that a combination of questionnaires addressed to specialists and to a random population sample could be the best method of estab-

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornwall, 1986</td>
<td>UK</td>
<td>9%</td>
</tr>
<tr>
<td>Callam, 1987</td>
<td>Scotland</td>
<td>22%</td>
</tr>
<tr>
<td>Baker, 1991</td>
<td>Australia</td>
<td>22%</td>
</tr>
<tr>
<td>Salaman, 1995</td>
<td>UK</td>
<td>9%</td>
</tr>
<tr>
<td>Nelzen, 1996</td>
<td>Sweden</td>
<td>9%</td>
</tr>
<tr>
<td>O'Brien, 2000</td>
<td>Ireland</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

From G. Guarnera.\(^3\)
lishing the real prevalence of skin ulcers. Presently available data show a prevalence of ischemic ulcers varying from 9% to 22% (Table II).3

References

CLINICAL EXAMINATION
If well conducted, the clinical examination is generally sufficient to make a diagnosis of ischemic ulcer and critical limb ischemia. A proper clinical examination is not possible without an accurate and complete medical history which, naturally, must not be limited to the study and evaluation of the vascular situation, but must be oriented to the search for possible risk factors including arterial hypertension, diabetes mellitus, hyperdyslipidemias, tobacco use, thrombophilic conditions and coagulation disorders, intake of estrogen/progestins etc. and the presence of any related pathologies such as cardiopathies (ischemic, dilated, sclerotic-hypertensive), cerebrovascular pathology, respiratory diseases, polycythemia, renal failure, etc.

A careful medical history must be followed by an equally accurate physical examination that must include a systematic passage through the classical portions of physical symptomatology, with particular regard to inspection, auscultation and palpation.

It is fundamental, before the regional clinical examination, to carry out a general physical examination and a physical examination of the individual organs and systems, aimed at excluding clinical pictures attributable to cardiac, internal medicine, metabolic, renal or neurological pathology (arterial hypertension, heart failure, arrhythmias, diabetes mellitus, chronic renal failure, cerebral vasculopathies, neural radiculopathies, etc.) that condition and/or aggravate the peripheral vascular disease.

The observation of the skin of an ischemic limb, of its coloring (pallor, cyanosis, erythrosis), of possible variations in relation to posture (acral pallor in decubitus), of trophism and of alterations of the skin adnexa (dystrophy of the skin, absence of hair and onychodysplasie), the presence of trophic lesions in acral locations or, according to the location, of an angiosomic type, scars from previous ulcerative lesions and the outcomes of minor and major amputations, the absence of arterial pulses upon palpation at the brachial-antebrachial landmarks, at the inguinal site, in the popliteal area and at the common subpopliteal landmarks, the palpation of pulsating masses in the abdomen, the detection through auscultation of “indigenous” murmurs in correspondence with the anatomical auscultation sites such as the lateral-cervical regions, the supraclavicular fossae, the inguinal regions, Scarpa’s triangle, the popliteal compartment, etc. confirm the suspected diagnosis of arteriopathy.

Instrumental and laboratory diagnostics
Ultrasound examinations
The execution of a basic instrumental parameter that is extremely important for discriminating between healthy patients and patients with pathology must follow the classical physical symptomatology: the ankle-brachial index (ABI according to the known Anglo-Saxon acronym or the Winsor Index), which precisely expresses the relationship between the systolic pressure value measured at the ankle and the systolic pressure value measured at the humerus on a patient at rest, in the supine position. The reading must be performed on both limbs during the first visit and checked in case of a change in the clinical picture. It is
appropriate to measure the two pressures at the same time, in consideration of the variability that can be encountered in the first minutes of detection with relation to the patient’s movements. If not performed by experienced personnel and with the required accuracy, the ABI reading can have rather high “intraobserver” variability.

Paradoxical ABI results (values greater than 1.3) can emerge in patients with incompressibility of the arterial walls, as in the case of diabetics or in those with medial calcinosis (Monckeberg’s disease). The continuous wave Doppler examination still retains its validity for diagnostic purposes for the measurement of the segmental pressures of the transversal pressure gradients between the healthy limb and the limb with stenotic-obstructive lesions and for dynamic tests during the study of irroration prevalences of the palmar and plantar arches. A portable device is sufficient for the ABI reading (Figure 1).

The color-Doppler ultrasound, a method with the advantages of being non-invasive, low-cost, reproducible, and having high specificity and sensitivity, and with the only limit of being an operator-dependent method, is used to locate the site and assess the severity of the arterial lesion responsible for the clinical manifestation and to exclude a possible ectasia pathology borne by the arterial region in question. It is an instrumental investigation that should not be used routinely in the vascular diagnosis of the lower limbs while, on the contrary, it is indicated in the morphological study of the femoral bifurcation and the superficial femoral and deep femoral segments and as an evaluation prior to angiography in cases in which a revascularization surgery is hypothesized. After angiography it provides useful details for the surgical treatment, since it can give useful information such as the caliber, characteristics of the arterial wall, morphology of the saphenous vein to be used for the by-pass, and the mapping of the collateral and perforating circulations in the case of the in situ surgical option. The use of color-Doppler ultrasound as a replacement for the angiographic investigation does not seem rational, as the ultrasound method lacks homogeneous execution criteria and still has operator-dependent reporting (Figure 2).

**Radiological examinations**

As known, angiography is an invasive contrast investigation that is moreover burdened by a significant rate of morbidity (serious reactions to contrast media in 0.1%) and mortality (0.15%), even if the use of non-ionic contrast materials, the quality of the devices for the introduction of the media, and digital
image subtraction techniques have contributed to significantly reducing complications. However, for these reasons, angiography is only indicated in those patients with critical limb in which there is an indication for surgery, and maintains the role of the intraprocedural method of choice during invasive therapy, of both the traditional and above all endovascular types, in a completely prejudiced and codified way.

CT angiography and MR angiography are invaluable investigations in the study of patients in which a dilatative and/or desiccating pathology is associated with the stenotic-obstructive pathology responsible for the hypoperfusive finding. In recent years, in vascular surgery, the spiral CT scan with three-dimensional image reconstruction has acquired an important role, as it is a method that allows a very accurate definition of complex pictures.

**Complementary investigations**

In the clinical-instrumental course of evaluation of patients with critical limb, there are other complementary investigations that are extremely useful due to their predictive significance on the possibility of healing trophic lesions and for evaluating the optimal level of amputation. These examinations are the detection of the segmental systolic pressure, transcutaneous oximetry, laser Doppler, and capillaroscopy. The measurement of the segmental systolic pressures provides quantitative information on the hemodynamic significance of the arterial lesions.

The detection of the transcutaneous oxygen (TcPO$_2$) and carbon dioxide (TcPCO$_2$) tensions offers useful data for a metabolic evaluation of the ischemic tissue. These parameters represent an important instrument for the prediction of the healing of an ischemic ulcerative lesion; partial oxygen tension values less than 20 mmHg are a limit of therapeutic failure while 40 mmHg are predictive of possible healing.

Laser Doppler is less used for diagnostic purposes; it finds its rightful place primarily in pathophysiology clinical research and studies. Capillaroscopy, which is specifically mentioned elsewhere in this document, finds a unique indication in the diagnostic confirmation of ischemic trophic lesions during scleroderma (Figure 3).

Oscillography and plethysmographic investigations are to be entirely proscribed, as they are now obsolete diagnostics.

**Clinical-diagnostic approach to the ischemic ulcerative lesion**

The clinical process remains the most important one also with regard to the diagnostical approach to ulcerative lesions in the context of the nosographic finding of chronic critical ischemia (Leriche-Fontaine stage IV – Rutherford degree III, cat. 5-6). In fact, a careful clinical-morphological examination of the lesion allows the confirmation of the diagnostic direction through the evaluation of the classic parameters represented by the size, depth, shape, number, site, and border and background characteristics and by the examination of the perilesional skin. The ischemic ulcer usually has a pale background with little granulation tissue, irregular margins and edges that are often necrotic, inserted in a context of perilesional skin with marked dystrophic manifestations (loss of the normal pilifer assets and ungual alterations). The regional and perilesional skin looks pale, and is often characterized by ecchymotic marbling and/or diffuse cyanosis.
Edema from the forced antalgic declivous position frequently coexists, and is particularly feared in the arteriopathic patient with regional insufficiency because it triggers a vicious cycle of tissue suffering that progressively aggravates the perfusion deficit and the metabolic exchanges on the microcirculation. The site of the ischemic ulcerative lesions can be acral (toes), localize to the heel, have a mechanical genesis “from pressure” on an arteriopathic base (and thus be localized to areas subjected to prolonged tissue crushing), or have a typically “vascular” disposition in the sense that it can localize to the distribution area of an artery that feeds that area (anterolateral region of the leg, heads of the first and fifth metatarsal, plantar surfaces). The concept of angiosome is thus introduced to indicate the anatomical units characterized by a specific and readily identifiable vascularization. The leg’s three distribution vessels (anterior tibial artery, posterior tibial artery and peroneal artery) “feed” six distinct angiosomes at the ankle and the foot. A correlation is demonstrated between vasal obliteration and localization of the ulcers, and this allows the surgical treatment to be directed in an elective manner toward the vessel that is at the origin of the regional perfusion deficit.

The clinical examination therefore does not deviate from the usual path that must be followed in every wound care patient with regard to the ulcer’s evaluation. The site must be evaluated for the pathophysiological reasons described previously, the shape and the number, the background (coloring, presence of signs of bacterial contamination or colonization, granulation centers, necrotic eschars), the skin and more generally the skin adnexa and the perilesional tissues, the presence of pain, its characteristics and the modalities of occurrence, and the possible presence of olfactory peculiarities related to tissue necrosis.

The clinical-diagnostic approach to patients with ischemic ulcer is essentially based on four elements: 1) medical history; 2) clinical-morphological examination of the ulcer and perilesional skin; 3) vascular symptomatological examination; 4) laboratory-instrumental study (Figure 4).

In the clinical-diagnostic path of the patient with a critical limb and ischemic ulcerative lesion, the laboratory represents a precious support for the clinical monitoring of the patient and for the application of correct and targeted therapeutic options of both a systemic and topical class.

The reference is to the control of the routine laboratory parameters to show any infections (leukocytosis, sedimentation rate), alterations in glucose metabolism, protein levels, renal function and myocytolysis parameters.

A frequent and relevant problem from the clinical point of view is bacterial and fungal colonization of ulcerative lesions; the appearance of signs and symptoms that can be correlated with the presence of an infection including fever, pain, lymphangitic involvement, extension of the lesion or delay in scarring, coloring of the background, and worsening olfactory modifications must be orienting towards this complication, particularly in lesions with a primitively ischemic genesis. In these cases it is extremely important from the pathophysiological point of view to identify the responsible microbial agent through targeted microbiological surveys such as the culture test, which is now standardized and reproducible. This examination allows the isolation of any pathogenic agents and the evaluation in vitro of the antimicrobial agents most appropriate for the treatment.
The peripheral arterial insufficiency, causing the tissue damage in the peripheral arteriopathy, is provoked by a reduction in the blood flow, determined, in 80-90% of cases, by the presence of atherosclerotic plaques (Figure 6).

The atheroma is the location of platelet aggregation and of coagulation cascade activation causing alterations in the blood flow. The vessel’s haemodynamics becomes altered: the blood flow velocity at stenosis level increases proportionally to the severity of the lesion, diminishing significantly the further down the lesion is located together with arterial pressure. The endothelium performs a basic role in the microcirculatory homeostasis in that with the production of several molecules it actively participates in the haemoreological and coagulative processes. The macrocirculatory alterations determined by the atherosclerotic disease effect the microcirculation.

In microcirculation there are at least two systems giving rise to the local regulation of the flow. The microvascular flow regulating system (MFRS) is always active, with the production by the endothelium of some molecules with both a vasodilatation and a vasoconstrictive action, in the local regulation of micro-haemodynamics, including the skin. Prostacyclin, nitric oxide, EDRF and tissue plasminogen activator are only some of the molecules produced by the MRS system regulating the blood inflow into the microvessels.

The microvascular defence system (MD) is the other system involved in circulatory microregulation. It concerns molecules and soluble receptors and membranes produced by the endothelium, but above all by the circulating cells (leukocytes and platelets), in a broad reply to a “threat” which can disturb the microcirculatory homeostasis, which on the whole activate the platelet aggregation and promote vasoconstriction (DCF, thromboxane A2, serotonin, coagulation factors, PAI, endothelin). These two regulatory systems are normally in homeostatic balance between activators and re-

**References**


**Figure 5.—Infection and in vivo evaluation.**

**PHYSIOPATHOLOGY**

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MOLLO

with ischemic skin lesions be they ulcers or gangrene, with symptoms and indications being present for at least two weeks, as attributed to a demonstrated arteriopathy.\(^3\)

A subgroup of patients does not fall within this definition, in that it comes with a serious peripheral arteriopathy with reduced pressure of perfusion at the ankle joint, even if this is asymptomatic. These patients, suffer from “chronic subclinical ischemia”, owing to their sedentariness do not have claudication, have a reduced perception of pain due to diabetic neuropathy and are at high risk of progression of the pathology, since they have the same local and systemic outcomes as patients with full-blown CLI.\(^2\)

The trophic lesions (ulcerations and/or distal gangrene) often follow microtraumatisms and could interest the distal extremity with digital or interdigital localisations. The sensory neuropathy typical of diabetic persons worsens the clinical picture since, owing to reduced skin sensitivity and to reduced sweating, it could determine fissures of the dry skin, an increase of arteriovenous shunt and the evolution towards an ulcer-gangrene clinical picture, although paucisymptomatic (Figure 7).

The onset of critical limb ischemia (CLI) occurs when arterial stenoses or occlusions reduce the blood flow to the extent that, notwithstanding the compensation mechanisms (formation of collateral circulations, activations of vasodilatory and antiaggregant factors), the nutritional needs of peripheral microcirculation could not be ensured, even at rest.

In its classical definition the CLI is a manifestation of the chronic peripheral obstructive arteriopathy inflicted on patients with chronic ischemic pain at rest or patients with ischemic skin lesions be they ulcers or gangrene, with symptoms and indications being present for at least two weeks, as attributed to a demonstrated arteriopathy.\(^3\)

The presence of the diabetes mellitus worsens the clinical picture of the critical ischemia and of the peripheral arteriopathy. Some 15% of diabetic patients develop a foot ulcer (more likely in the sole and toes), while from 14% to 24% undergo an amputation. The accompanying neuropathy
be more efficient if the analgesic is administered regularly according to the WHO scale for pain control.\(^5\)

In some selected and refractory cases an implant of spinal cord stimulators (SCS) could be required for pain therapy. Cord stimulation (spinal cord stimulation) induces an inhibition of nociceptive sensitivity and is thus an analgesic. The mechanisms through which electro-stimulation applies its antalgic effect have not yet been made clear at all.\(^6,7\)

The anxiety-depressive component often found in patients with CLI also requires the use of anti-anxiety drugs and antidepressants (Figure 8).

Although revascularization constitutes the best option, where indicated, it could not overlook an intensive medical treatment preceding, accompanying and following the said revascularization to guarantee better results in terms of healing ulcers, of amputations and of survival.

The drugs which are recognised and validated for the treatment of critical ischemia are the prostanoids, iloprost (a stable analogue of PGI\(_2\)) and PGE\(_1\) (alprostadil). No other drugs are available which could be alternatively used (TASC II).

Iloprost performs its action by inhibiting the production and release of TXA\(_2\), PDGF and factor V of the coagulation; it besides inhibits adherence and limits the tissue damage caused by the aggregation of leukocytes and platelet, while its more evident and more immediate action lies in vasodilatation. It Besides interacts with the NO, inhibiting the adherence and endothelial permeability, interacts with the build-up of leukocytes in the ischemic location, inhibits the interactions between endothelium and phagocytes, reduces the levels of T-lymphocytes and cytokines, reduces the levels of ICAM-1, reduces blood viscosity and finally takes part in the angiogenesis mechanisms through an increase in VEGF levels.\(^8,9\)

Iloprost administered during femoral-distal reconstructions allows a marked reduction in peripheral resistances, in a significantly superior manner to alprostadil, though with major collateral effects (Figure 9).\(^10\)

Recently a few scientific Associations contributes to the occurrence of the typical osteoarticular deformities of the diabetic foot.\(^4\) Clinically the opening of several arteriovenous shunts could be the cause of objective evidence of a warm foot, while caring for the distal arteries and the microcirculatory area could lead to the discovery of an “eusfigma” of the tibial pulses (with normal ABI or exceeding 1).

**Pharmacological therapy**

In consideration of the variety of onset clinical pictures, of the multi-area localisation of the atherothrombosis, of associated comorbidities, of possible therapeutic options (medical-surgical-endovascular) the approach made to the patient should be as early and multidisciplinary as possible.

Given that the reduction of the incidence and severity of critical ischemia (ulcers and amputations) could not overlook an early diagnosis of chronic peripheral obliterative arteriopathy and an aggressive management of the risk factors of atherothrombosis, the objectives of CLI treatment are: to resolve ischemic pain, to heal ischemic ulcers, to avoid limb loss, to improve functional ability, to improve the patient’s quality of life and life expectancy.

The first step is to treat the pain, be it localised in the skin or in deeper tissues (joint, muscular, bone). Revascularization improves the pain. The control turns out to
Rehabilitation methods and programmes

The rehabilitation of patients suffering from CLI envisages the activation of specific rehabilitation programmes, in which controlled physical activity constitutes the main methodology used. Rehabilitation programmes are adopted according to deambulation protocols only for those patients in whom trophic lesion healing was obtained as well as the passing from an advanced stage of arteriopathy (stage III, IV) to a less advanced stage (stage IIB, IIA).

Patients are advised to run a daily specific track, under controlled speed and in-
clination, or, if they can attend at a vascular rehabilitation outpatients' department, to perform deambulation exercises on a treadmill. Some protocols envisage 15 controlled physical exercise sessions each lasting about 30 minutes. The distance to be run equals about 70% of the patient's deambulatory capacity (painless interval walking) with a 10% inclination and a speed of 3.2 km/h. Each exercise is spaced out over a recovery period equivalent to the recovery period, after maximum exercise, necessary for the disappearance of pain after the exercise is stopped. The reason is to increase walking autonomy by training and the development of collateral circulation. For the same purpose exercises could also be undertaken for the improvement of walking techniques, deambulatory capacity and posture.

Patients who instead present trophic lesions such as to prevent proper deambulation, should undertake the rehabilitation even if enticed by the performance of specific programmes featuring the execution of active and passive rehabilitation exercises to improve limb effectiveness and muscle tone. These activities, at least initially, must be repeated on a daily basis, through the support given by the physiatrist and/or physiotherapist.

Rehabilitation also envisages the support of psychologist specialists, who should allow the patient, during the various stages of the disease, to overcome specific psychological blocks which could influence the therapeutic effects of the given therapy.

The purpose is that of developing an integrated system of therapy/rehabilitation, by minimising the effects of the cure's fragmentation. Moreover, the identification of some psychological factors could be useful to increase adherence to treatment by drugs, through psycho-educational interventions and by psychologically sustaining the patient.

Since some psychological variables are strictly connected with amputation interventions, the treatment of the psychological component assumes a fundamental position in favour of interventions which sustain the patient in adapting oneself to the loss of a limb.

### BOX 1

Therapy aims in severe arteriopathy:
- to resolve ischemic pain
- to heal ulcers
- to avoid limb loss
- to improve the patient's quality of life
- to prolong life expectancy.

### BOX 2

- Revascularization should be considered in therapeutic strategy, taking into account the risks linked with the intervention, be they surgical or endovascular, the anatomical-functional nature of the altered vessels, run off, comorbidity, the patient's life expectancy and the functional recovery capacity of the limb suffering the ischemia.

### BOX 3

- The chronic critical ischemia of the lower limbs can obtain benefit from an integrated medical-surgical-rehabilitation treatment.
- The association of several therapeutic options determines a synergic effect on the improvement of the clinical picture and on the patient's quality of life.
- The intensive treatment is based on the use of active drugs on the microcirculation system (prostanoids, antiaggregants, anticoagulants, haemorheologicals) associated with analgesic treatments (pharmacological painkiller or by using SCS) and with ongoing clinical and instrumental monitoring, to be performed in a specialist environment.
A primary and secondary prevention of cerebro- and cardiovascular events should be performed (with antiaggregants, statines, ace-inhibitors).

Association of accompanying co-morbid vascular therapy (carotidopathies, aortic abdominal aneurysms, ischemic heart disease etc.) and otherwise (chronic respiratory and renal insufficiency etc.).

Intensive angiological treatment in specialist structures dedicated to patients suffering from chronic critical ischemia constitutes an alternative to early amputation.

In a chosen sample of patients who cannot be revascularized evaluate the neo-angiogenic therapy option, above all by using the progenitor cells of the endothelial cells through in situ differentiation of autologous stem cells.

References

SURGICAL TREATMENT

The basic treatment of critical limb ischemia consists in surgical or endovascular revascularization, with the main aim of saving the limb.

In therapeutic strategy one need consider the angiosome concerned and collateral areas.

The angiosome concept was introduced towards the end of the eighties to identify anatomical units with their own specific vascularization. With regard to the ankle joint and the foot six distinct angiosomes have been identified, as supplied by the three leg arteries (posterior tibial artery no. 3; anterior tibial artery no. 1; peroneal [fibular] artery no. 2), with a possibility of anastomosis and connections between adjacent areas. These anatomical studies have allowed correlating the localisation of ulcers with the stenotic or obstructed vessel and addressing the surgical intervention of revascularization selectively towards the vessel which supplies the angiosome where the lesion is located (Figure 11).

A high percentage of trophic lesion healing and limb saving (between 70% and 90%) can be obtained in case of surgical or endovascular revascularization of vessels directly supplying the damaged angiosome. In case of adequate interconnections, even the revascularization of the feeding artery of the adjacent angiosome could cause the healing of the lesion (in 60-70% of the cases).

Such data are confirmed by a recent work which has shown the positive influence on the healing of ulcers of an adequate collateral distal circulation after a revascularization procedure. Seventy-six ischemic ulcers, classified according to the angiosome concept, have been followed after a revascularization intervention of a single vessel. After twelve months of follow-up

![Figure 11.](image-url)

Figure 11.—According to the anatomical concept of angiosome, the localisation of an ulcer leads back to the vessel where the lesion is located. (From: Guarnera G. Le ulcere vascolari degli arti inferiori - Vascular ulcers of the lower limbs. Salerno: Momento Medico Ed.; 2011).
the percentage of lesion healing in case of direct revascularization (92%) was higher in respect of cases of indirect revascularization (73%), but similar to cases in which indirect revascularization was supported by a rich collateral circulation (85%).

In a recent review of 249 patients, suffering from limb ischemic lesions and who underwent a distal bypass, a total percentage of healing of ischemic ulcers was obtained of 84.7%, with lower values in cases of indirect revascularization, only in patients with chronic kidney failure.

In this study the localisation and the extension of the ulcers and the comorbidities appear to be more important than the angiosome concept in terms of lesion healing.

Adversely, another recent review of 369 patients who underwent an endovascular procedure for a subpopliteal lesion has documented the importance of revascularising the feeding artery of the pathological angiosome in terms of limb saving and the prevention of major amputations.

From a technical point of view the revascularization could take place with an endovascular procedure or with a surgical bypass intervention. The TransAtlantic Inter-Society Consensus has identified the profile and the extension of the vessel lesions as reference parameters in choosing between the two methods, while the BASIL trial shows the benefits of the traditional surgery for patients with a life expectancy exceeding two years, besides emphasising the importance of an autologous vessel as an ideal conduit for a bypass.

Generally speaking, the more widespread therapeutic attitude consists in reserving traditional surgical therapy to extended lesions of the aortoiliac area, of the common femoral and superficial femoral arteries and the endovascular treatment of isolated lesions of the iliac arteries, of the superficial femoral artery and of the subpopliteal vessels.

For the purposes of lesion healing, one should finally consider that it is often necessary to adopt a series of post-revascularization procedures (debridement surgery, minor amputations, VAC therapy, skin grafts).

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**BOX**

— The main aim of the surgical treatment is limb saving
— In the therapeutic strategy account need to be taken of the involved angiosome and collateral areas
— Endovascular procedure should be the first-choice method, while traditional surgery could be reserved for lesions which are technically not appropriate for angioplasty
— The endovascular procedure and revascularization surgery are often complementary

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LOCAL TREATMENT OF ISCHEMIC LESIONS

Topical treatment has a non secondary role in patients suffering from ischemic ulcers of the skin and it should be supplemented to systemic drug and surgical treatment. Actually, any improper action might compromise the healing of an ischemic ulcer rendering useless proper therapeutic medical/surgical management.

A mistaken local treatment could however determine amputation as a result, even if a technically perfect revascularization intervention has been performed. Awareness of the principle regulating the local management of chronic skin lesions would allow a further improvement of the clinical results in patients with critical ischemia and a consequent reduction in amputation rates.

Local treatment follows some basic rules which are still valid for the various clinical forms of ischemia.

Ischemic lesions could present themselves as:
— ulcers localised in various, often multiple, areas with variable impairment of surface and deep tissues;
— dry gangrene or moist gangrene;
— ulcers as sequelae of revascularization surgical interventions, or of amputation;
— acral ischemic lesions in the sclero-derma areas, in patients with an arterial disease embolic disease or with Raynaud’s disease or suffering from perniosis etc.

Prior to revascularization, when this is indicated and possible, the ischemic ulcers should be treated with a non-adherent gauze associating a reduction of the pressure load ¹ which could be made, in the lower limbs, by altering the shoes, orthopedic shoes and plaster casting techniques depending on the locality of the ulcer and the seriousness of the ischemia.², ³

Following revascularization it is even more important to reduce the “load” and avoid the repetitive traumas caused by foot-wear. Without such devices one would take the risk of jeopardizing the beneficial effects of revascularization.

All authors associate the concept of “good clinical practice” with the possibility of using a “range”, the widest possible, of technological products for the treatment of the trophic lesions.⁴

If used well, according to pre-set protocols, the possibility of choice of technology becomes a resource in itself for the containment of health expenses as long as there would be, on the part of users, an in-depth awareness of the clinic, techniques and materials.

The basic technologies sustaining proper management of the skin lesion, further to its etiology, could be thus, partially, summarised:
— fast and selective debridement;
— topical antimicrobials for the prevention of the recurrent septic episodes (ionic Ag, nanocrystalline Ag, PHMB) in combined action dressings;
— negative topical pressure;
— control of procedural pain;
— FREM, PESF;
— compression therapy;
— growth factors;
— use of dermal substitutes or of cadaver skin;
— preservation of the perilesional skin.

The possibility that the clinician can make use of available advanced technologies widens the clinician’s possibility of interventions and improves the patient’s healing expectancy.

Fast and selective debridement

While the debridement of neuropathic ulcers in a diabetic person could be surgically performed without any hesitation, in ischemic ulcers and critical ischemia ulcers, particularly, it should be assessed whether
to proceed with enzymatic or autolytic debridement, which is less painful and less traumatic. Atraumaticness is a prerogative which should always be taken into account when healing an ischemic skin ulcer.

After every intervention of debridement, the lesion is frequently dressed, if possible daily, having first irrigated it or footbathed it with tap water and small amounts of soapy solutions (e.g., chlorhexidine 1%), or with a sterile physiological solution.5

As soon as the local signs of inflammation and infection fade, the dressings could be applied every two or three days by applying, after irrigating with water, the most suitable combined action advanced dressings, chosen on the score of local conditions.

There are no comparative studies on surgical cleansing, with respect to between enzymatic or autolytic, but experts are unanimous in retaining that cleansing is essential in case of callus and necrosis and that surgical debridement represents the best choice when one can practise it.

In the most recent guidelines emphasis has been made on the precocity of debridement interventions with the removal of the tissue defined as “non active”, highlighting the time factor; debridement should be the fastest possible and performed the soonest possible. It is considered, above all in ischemic ulcers, as the most efficient action in the abatement of the bacterial load of the skin lesion.6

Topical antimicrobials for the prevention of recurring septic episodes in combined action dressings.

Treatment with advanced dressings should be reserved, according to TASC II, to ulcers in patients who have already been revascularized according to the basic principles of the “Wound Bed preparation”.4 Much emphasis is laid on the role of the bacterial population present in the bed where the ischemic ulcer 5 is found and above all the role of the staphylococcus aureus representing about 30% of the causes of infection; polymicrobial infections turn out to constitute about 40% of the total.7 The infections are considered as extremely dangerous, above all in diabetic patients, because they precede amputation in a percentage of cases which, in the presence of osteomyelitis, could reach 40%. For this reason targeted systemic antibiotic therapy is not considered to be sufficient, and it is emphasized as very important to associate very early procedures such as surgical toilet and drain, followed by an antibiotic therapy which is targeted and prolonged in time. All this would be in preparation for any revascularization intervention. Wherever has already been revascularized, or in patients in whom revascularization cannot take place, a surgical or hydrosurgical debridement of the ulcer is performed and subsequently treatment with advanced dressings and/or with technologies suitable for the clinical status of the skin lesion.

Even if there is at least one clinical study witnessing to the effectiveness of enriched dressing with ionic silver in accelerating the healing of chronic lesions and another study on the effectiveness of cadexomer iodine, there do not exist in literature any definitive proofs of the effectiveness of dressings with antiseptics, although these are abundantly used in day to day practice and show, in some studies, certain advantages and are lower priced.8

The concept of the “recurrent septic” has, however, been recently introduced and this corresponds to the stages where a failure occurs, in the clinical history of skin lesions, in the healing process set in course by an increase in the bacterial load of the bed where the ulcer is found. It is exactly in the presence of recurrent septic episodes that authors confirm the effectiveness of the dressings with antiseptics.9 This could be the definitive arrangement in this type of advanced dressings for the management of ulcerative skin lesions.

**Negative topical pressure**

In those lesions where exudation could not be controlled with absorbent dressings, use can be made of negative topical pressure, above all in the diabetic foot and in lesions after partial amputation.10
Unfortunately, a review of current literature does not presently furnish any proofs which can affirm that such technology can accelerate the healing processes of ulcers. Moreover, negative topical pressure is much more resorted to, to the greater satisfaction of operators and patients alike.

Some scientific pharmacoeconomic workers have shown that the use of these dressing systems leads to a decrease in financial and company costs in the administration of patients suffering from lower limb ulcers; unfortunately these studies are not considered to be useful to obtain any recommendation for use at a higher level.\textsuperscript{11}

**Pain**

Pain control in patients with ischemic ulcer is extremely difficult and is exasperating when dressings are changed. The pain caused by the procedure requires various stratagems about which reference is made to the EWMA position document of 2004.\textsuperscript{12} The release of FANS through advanced dressings (polyurethane foams) could contribute towards reducing the pain in some “responder” patients in vasculitic ulcers, where there exists a strong inflammatory component, and in ischemic ulcers, above all those which are scleroderma with a sufficient exudate component.\textsuperscript{13}

**FREMS and PESF**

Pain control could be, in some patients, realised by using the FREMS therapy (Frequency Rhythmic Electrical Modulation System), a comfortable methodology which is easy to apply and is well accepted by patients. Pain reduction, in responder patients already occurs after 24-36 hours and the healing rates are speeded up. Even this technology lacks relevant clinical studies.\textsuperscript{14} The PESF, namely the use of the pulsating electrostatic fields, acts by improving the deformability of the red globules and the ability to re-establish the best hematic pH, by regulating arteriolar activity; it has the characteristics to be able, in the short term, to be a treatment technique in aid of the recovery of the microcirculatory homeostasis in patients with critical chronic ischemia,\textsuperscript{15} and the consequent speeding up of healing processes of ischemic ulcers.\textsuperscript{16}

**Dermal substitutes**

A net reduction in pain is generally obtained after the application of a grafting of artificial skin (bovine or shark acellular dermal matrix or silicon supported horse collagen) or of cadaver skin. The artificial skin could also be used on avascular surfaces (covers of tendons and bones) in that it is colonised by new vessels deriving from nearby tissues. These surgical techniques are considered in ischemic ulcers only after revascularization or in cases of stabilised critical ischemia which could not be revascularized after intensive drug treatment with Iloprost. Bioengineered skin is very useful in scleroderma patients and in some cases of a diabetic foot, also after partial amputation. When the vascularization is completed the silicon is removed and, if necessary, an autologous grafting is proceeded with. It appears that the repaired skin with this system is more elastic and functional with respect to the procedure with homologous skin.\textsuperscript{17, 18}

**Compression therapy**

In patients with skin ulcers caused by critical ischemia associated with peripheral oedema, the use of sequential pressure therapy at low pressure (20 mmHg) is associated with an improvement of the trophic lesions for the resolution of the edema. Bandaging could be practised with these patients, but only by expert personnel: it should be anelastic and at low pressure.\textsuperscript{19}

**Growth factors**

The re-epithelization stage, above all if the revascularization procedure was suc-
cessful, could occur spontaneously in small sized ulcers. Larger ulcers could require the use of some further applications such as the growth factor of granulocitary derivation (granulocyte-colony stimulating factor, G-CSF) and the growth factor of platelet derivation (platelet-derived growth factor (PDGF)-BB human recombinant). 20, 21

**Perilesional skin**

Perilesional skin in patients with peripheral ischemia show up as dry and dehydrated. The use of softening creams is particularly useful in preserving it because it avoids the formation of cracked skin which is often at the base of the formation of new ulcers. Skin dryness and xerosis decrease cellular migration and the deposition of extracellular matrix, altering the repair process. 22

**References**


**OTHER TREATMENT OPTIONS**

The patient with critical lower limb ischemia is a natural candidate for revascularization surgery aimed at saving the limb. Use of other types of treatment is justified only in case of contraindications to the surgery that can be general (patients in critical condition or with multiple pathologies that contraindicate surgery) or local (distal stenotic-obstructive pathology that is not susceptible to revascularization) or in case of failure of the surgical and/or endovas-
cular therapy. It is primarily based on the pharmacological therapy discussed in the previous chapters and on treatments that are complementary to medical therapy.

Compression therapy, spinal cord electrical stimulation and hyperbaric oxygen therapy may number among these.

**Compression therapy**

The rationale of compression therapy in chronic obstructive arteriopathy is well known: the treatment of a possible coexistent venous pathology, skin ulcers, and edema that aggravates the arteriopathy.

Compression therapy is possible in patients with chronic obstructive arteriopathy, also with an ankle brachial pressure index (ABI) reduced down to 0.5-0.6.

Numerous clinical studies and guidelines do not exclude the possibility of using a modified compression, “lighter” than what is generally practiced, when the ABI is between 0.5 and 0.8. In this clinical situation, not only is the pressure at the big toe not reduced but an increase in the peripheral blood flow below the compressive system may be encountered. In one of our works in patients with mixed-etiology ulcers and an average ABI of 0.6, we were able to demonstrate that the arterial flow under the bandage increases when it is applied with a pressure of 20-30 and also of 30-40 mmHg; the arterial flow begins to go down again when the pressure of the bandage rises further to 40-50 mmHg while always remaining above the baseline values. Obviously the utmost care is always given so that the pressure of the bandage is significantly lower than the systolic pressure of the ankle. The increase in flow registered under the bandage may be induced by the reduction of the transmural and venous pressures, which induce an increase of the arteriovenous gradient, but also from the release of vasodilating substances together with a reduction of pro-inflammatory mediators that occur at a microcirculatory level.

The condition of critical ischemia and skin ulcer is very different from critical ischemia. In this condition the pressure at the ankle is, by definition, less than 50 mmHg, the value that contraindicates any continuously-applied compression therapy.

However, in these conditions, intermittent pneumatic compression therapy (IPC) has been shown to play a relevant role, being able to increase the arterial flow not only in normal patients but also in arteriopathic ones.

Even though IPC administration methods and times vary depending on the studies, in arteriopathic patients with critical ischemia, there tends to be a very high pressure (around 120 mmHg) that is rapidly reached and maintained for a few seconds. Fifteen to 20 seconds pass between one cycle and another; the administration modality is, therefore, very different from that generally used in IV-lymphatic pathology for edema reduction. The first studies on IPC in the claudicating patient go back 20 years ago and reported beneficial effects on the distance of travel, symptoms, and the systolic pressure at both the leg and the arm.

Among the mechanisms that may explain the increase in arterial flow induced by IPC in arteriopathic patients, one is well-documented and is represented by the reduction in the venous pressure that increases the arterial-venous gradient and therefore the arterial flow, which can increase up to 70%. Two other mechanisms are hypothesized but until now have never been proven in a definitive way: the suppression of the venoarteriolar reflex which leads, again, to a reduction in venous pressure, and the increased release of nitric oxide from the vessel walls due to an increase in shear stress induced by IPC that can, in turn, lead to an increase of arterial flow. Also in critical ischemia, an increase of arterial flow with intermittent pneumatic compression was observed in retrospective studies that have shown: healing in 50% of cases of patients with ischemic ulcer and TcPO$_2$ <20 mmHg; an improvement in the ischemic ulcers in all patients, with any level of TcPO$_2$; the salvage of 9/14 ischemic limbs in inoperable patients.

At three months 58% of the limbs were
Subsequently the technique, first introduced into clinical practice in the management of pain syndromes refractory to conservative treatments, spread worldwide and was also routinely used for the treatment of vesical dysfunctions from multiple sclerosis, extrapyramidal-type motor disorders, and spasticity secondary to spinal cord lesions.

The rationale at the basis of SCS is primarily represented by the attempt to modulate the neural transmission of pain impulses from the periphery to the brain at the spinal cord.

According to Gate Control theory, which is still one of the most accredited, since the transmission of pain would be correlated to the balance of information that passes the spinal cord through the large-diameter Aδ fibers (non-nociceptive) and the small-diameter Aβ and C ones (nociceptive), if the activity in the large Aδ fibers prevails, the pain will be mild or absent (gate closed), but if transmission prevails along the thin Aβ and C fibers, the pain will be perceived (gate open).

Even if Gate Control theory is still the main hypothesis to explain the operation of SCS, in reality, the mechanisms of action implicated in spinal cord stimulation are multiple and therefore the exact mechanism remains unknown.

With regard to the effectiveness of the use of SCS in the treatment of chronic pain of an ischemic nature from serious peripheral arteriopathies, in 1976 it was postulated for the first time, following some observations of Cook et al. that noted, in patients subjected to SCS for neurogenic vesical, an increase of local temperature and an improvement of the tissue trophism of the lower limbs.

In critical ischemia the benefits on the arterial flow were observed at both the macrocirculatory level (increase of the flow evaluated with duplex on the popliteal artery and on the leg arteries) and on a skin microcirculatory level (laser Doppler on the dorsum of the foot). The mechanisms that induce an increase in blood flow are similar to those of the arteriopathic patient without critical ischemia and are substantially attributable to the increase of the arterial-venous gradient and production of vasodilating substances by the endothelial cells consequent to the increase in shear stress.

**Spinal cord stimulation**

The electrical stimulation of the spinal cord, defined by the Anglo-Saxons as spinal cord stimulation (SCS), was proposed for the first time in 1967 by Shealy, who used laminectomy in an attempt to treat uncontrollable pain syndromes. Dooley then proposed the percutaneous introduction of the stimulator electrode in the vertebral medullary epidural space in the treatment of various pain syndromes. Subsequently the technique, first introduced into clinical practice in the management of pain syndromes refractory to conservative treatments, spread worldwide and was also routinely used for the treatment of vesical dysfunctions from multiple sclerosis, extrapyramidal-type motor disorders, and spasticity secondary to spinal cord lesions.

In a more recent prospective study, 48 patients with an amputated foot due to critical ischemia and with open wounds were randomized into two groups in which the only difference in the therapeutic regime was the use, in one group, of intermittent pneumatic pressure. At 18 months from the start of the IPC therapy, the patients who received IPC were healed to an extent three times higher (58%) compared to patients that did not receive IPC (17%) and an equal proportion of the lower limbs had been saved (P<0.01). In another study with more cases, 171 patients were enrolled for three months. After 13 months the pain was significantly reduced and the pressure at the big toe and the popliteal flow were significantly improved. The salvage of the limb at 3.5 years was 94%.

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sions were contextually observed. Also in subsequent studies relative to patients with serious peripheral arteriopathies, the authors reported an excellent control of pain, observed an increase in healing of ulcerous trophic lesions, a decreased need for oral analgesics, and an improvement in the daily activities of the patients.34-39

In clinical practice the fundamental prerequisite for the proposal of a treatment with SCS in serious arteriopathies consists of the absolute or relative impossibility in these patients of a surgical and/or endovascular revascularization therapy, and of the more or less complete failure of previous invasive, pharmacological, or conservative treatments, and is based on the intent to correct the microcirculatory damage from low perfusion pressure secondary to the macroangiopathic hemodynamic lesions of an atherosclerotic nature that occurred upstream of the small vessels in time and in sequence.

Since, in critical lower limb ischemia (CLLI), the treatment of revascularization with invasive practices, including angioplasty or reconstructive surgery, is feasible only in 60% of cases, while another 20% of patients are obliged to undergo a primary amputation surgery at the time of diagnosis, the role of SCS can theoretically be carved out of the remaining 20% of subjects that, in the absence of alternatives, are subjected to temporary conservative adjutant therapies which, while not mechanically modifying the hemodynamic lesions of the macrocirculation upstream, are often able to limit the microcirculatory damage from altered perfusion pressure.40

In reality, given the high economic and professional cost of the method, the indications for the use of SCS should be restricted to only CLLI patients with limited trophic lesions (less than 3 cm in diameter), to subjects who are theoretically operable but at a high risk of failure of revascularization, or at a high operatory risk due to the presence of serious concomitant comorbidities, while the absolute contraindications are tied to the presence of extended trophic lesions (greater than 6 cm in diameter), of concomitant pathologies with short life expectancy (e.g., tumors) or serious pathologies of the dorsal lumbar spine (disc pathologies, vertebral schisis, serious kyphotic-scoliotic deformations, etc.).

Over the last decades, numerous clinical trials on the use of SCS were performed in arteriopathic patients with critical lower limb ischemia. Most of the work was carried out starting from the mid-80s and has, overall, documented favorable short-term effects of electrical stimulation on the salvage of the symptomatic limb and, sometimes, even a better long-term prognosis for patients in terms of morbidity and mortality.41-51

A really valid contribution to the selection of patients appears to be linked to the use of TCpO$_2$ both in a supine position and in declivity, allowing for a more precise identification of patients with a critical limb ischemia who are theoretically more responsive to therapy with SCS and are so eligible to the said treatment.51-55

In the course of past years there has been observed, both in our experience and in that of other important medical and/or vascular surgery centers, a sharp decrease in the number of patients with critical lower limb ischemia which cannot be operated on any longer and who so had to undergo an SCS, following probably, at endovascular intervention level, a major aggressiveness by doctors on distal arterial areas, previously excluded from procedures, and, at a medical level, of a wider use of infusion therapy with prostanoids in patients on whom, in co-administration with important comorbidities, vascular rehabilitation intervention could be immediately or absolutely contraindicated.56

Finally, on the basis of literature data and of our experience, epidural medullary electrical stimulation still seems to constitute to the present day a methodical alternative in treating critical lower limb ischemia turning out to be valid, scarcely invasive and reversible, but which to be successful requires suitable specialist competence by a medical multi-specialist team taking charge of the patient, not only in the performance stage of the procedure but also and above all in that of selecting patients and remotely following them up.

Although there has been a considerable
ISCHEMIC ULCER AND CRITIC ISCHEMIA

MOLLO

ischemia and the ulcers connected to it, as the ischemic tissues would benefit from hyperoxygenation with an improvement of the metabolism and a reduction of edema. Other effects that can be ascribed to hyperbaric oxygen therapy in the healing of ischemic ulcers would be: the stimulation of the proliferation and differentiation of fibroblasts, the increase in the formation and cross-linking of collagen, the stimulus for neovascularization, and the leukocyte-mediated bactericidal action.57

As a matter of fact, there are not many works on hyperbaric oxygen therapy in this indication while there are many reports of a good effect on the healing of ulcers with arteriopathy and diabetes, as is also shown by the Cochrane review.58

It is also interesting to note how, however, not all critical ischemia ulcers would be susceptible to improvement with hyperbaric oxygen therapy, but only those that show an increase in the $O_2$ tension equal to or greater than 10 torr while the patient breathes pure oxygen.59

In conclusion, as recommended by the Cochrane review58 and TASC II,48 some selected patients with an ulcer from critical ischemia are likely to benefit from hyperbaric oxygen therapy, but more rigorous studies are needed before a definitive confirmation of generalized efficacy can be made.

**References**

TREATMENT OF SCLERODERMA ULCERS

The first and earliest clinical manifestation of scleroderma vascular disease is Raynaud’s phenomenon, the change in the color of the fingers (but also feet, ears, nose, and tongue) mainly in relation to exposure to low temperatures, or, as is commonly described “a white finger, as if it were dead” as an expression of a phase of transient complete acute ischemia and spontaneous remission (Figure 12).

The nailfold videocapillaroscopy is a first level examination that can identify a pattern of alterations of the periungual capillary circle that are absolutely characteristic of a series of pathologies that constitute the so-called scleroderma spectrum, characterized by dilatations of the capillary loops with the formation of giant capillaries (megacapillaries) until the advanced forms where the microcirculation is completely disordered, with multiple avascular areas that constitute the capillary desert.

Digital ischemia is the most characteristic aspect of scleroderma vascular disease and is characterized by endothelial dysfunction that evolves in the intimal proliferation and is complicated by endoluminal thrombosis in the capillaries and arteries.

If not recognized and treated early, scleroderma vascular disease leads to real acute
and chronic ischemia of the fingers and toes with death of the tissues and formation of painful necrotic ulcers that are difficult to heal, and if not promptly recognized and treated with systemic pharmacological therapies and with local dressings, will inexorably evolve into gangrene.5-7

### Scleroderma ulcers

Ulcers are a visible evidence of scleroderma vascular disease. They develop in 30-50% of patients with SSc but we can say that they appear at least once in the course of the disease in almost all, and it is not unusual that the lesions arise before a definite diagnosis of systemic sclerosis has been made, especially if the diagnosis is delayed. Ulcers are not the most important complications *quo ad vitam* of the patient, while they represent the most debilitating complication for quality of life due to pain, functional impairment, long healing times and location with regard to the critical role that the hands play in daily and relational life. They occur relatively early in the course of SSc and have a chronic relapsing trend with devastating physical and personal, familial, and social psychological effects.1-6

They are typically ischemic ulcers as they are the result of a spasm and occlusion of the arterial-capillary region of the fingers, determining an ischemic and hypoxic damage that presents as a pitting scar, *i.e.*, localized hyperkeratosis on the distal phalanges up to dermohypodermic-muscular necrosis and acroosteolysis. The infections can have devastating consequences and evolve into amputations and sepsis (Figures 17).
A different aspect of scleroderma ulcers are the atrophic ulcers, that arise on the articular prominences, where the tissue is thinner and subject to traction as an outcome of cutaneous sclerosis and tendon retraction, and where the slightest occasional trauma inexorably results in trophic lesion without any tendency toward healing in the presence of atrophic sclerotic tissue and is often mechanically ischemized in tension on the articular surface (Figure 18).

Because of their slow tendency toward healing and long duration, atrophic ulcers are frequently exposed to infective phlogistic complications that further slow healing. Finally, in the course of systemic sclerosis, ulcers associated with an underlying calcinosis arise that trigger an intense inflammatory process like a reaction to a foreign body, absolutely finalized to the expulsion of the calcinosis itself, which determines the self-limitation of the inflammatory process and the healing of the lesion without concomitant infective complications (Figure 18).

The knowledge of the different types of scleroderma ulcers and of the different associated pathophysiological mechanisms is a necessary and indispensable prerequisite for the choice of the different targeted and effective therapeutic strategies; for example, the ulcer with underlying calcinosis may not be responsive to vasodilators like the ischemic ulcer should be.  

Primary prevention

The patient should be viewed in the familial context and should be educated and informed on the known pathophysiological mechanisms of his disease to guarantee a greater adherence and compliance with the directions given.

The patient must realize that he must keep his entire body warm (not only his hands) and avoid trauma to his fingers, he must stop smoking and taking vasoconstrictors (e.g., beta-blockers, adrenergic nasal decongestants) and caffeine, he must avoid exposing his hands to direct heat sources, he must constantly apply moisturizing and emollient creams, he must wear insulated gloves, even at night, he must know how to recognize the initial periungual trophic suf-
ferring and must have a priority, direct and fast access to the care center dedicated to scleroderma ulcers.\textsuperscript{9-11}

**Active ulcer therapies**

The treatment's objective is to promote the healing of the ulcer and reduce the formation of new ulcers. The optimal treatment should obtain the reduction of pain, the functional recovery of the hand, implement digital blood circulation and prevent infectious complications. The framing of the medical history and the careful evaluation of comorbidity are fundamental, as they can actively influence the ulcer's occurrence and complications such as diabetes, obstructive arteriopathy, and venous insufficiency due to the exponential additive impact of microcirculatory damage that requires a priority intervention on the macrocirculatory pathology where possible.

**Support therapy**

Pain must absolutely be treated not only as a primary and essential requirement of a global therapeutic approach aimed at the improvement of the patient's quality of life, but also as an essential requirement for the healing process, as the state of anxiety associated with pain evokes a vasoconstriction reaction that worsens and aggravates Raynaud's phenomenon and the consequent vasospastic ischemic damage. It is preferable to use acetaminophen and opioids instead of NSAIDs because of the pain's chronic characteristics and the need for prolonged treatments. Infection occurs frequently and the clinician must, every time he accesses the dressing, evaluate the occurrence of this feared complication, especially if the patient reports an increase in pain symptoms. If a purulent secretion can be detected, it is necessary to carry out a swab for culture and antibiogram examination, immediately starting an antibiotic coverage active against gram-positive bacteria, effective in most cases and possibly modified with the outcome of the antibiogram. Always ask for a radiological evaluation if you suspect that the infective phlogistic process may have affected the bone. Scleroderma patients may require further cycles of antibiotic therapy, particularly if an osteomyelitis process is present that requires parenteral and prolonged systemic antibiotic therapy.

**Pharmacologic therapy**

After having controlled the pain and infection, it is necessary to promote the healing of the existing ulcers and prevent the formation of new ulcers.

Despite the notable impact on the quality of life of the scleroderma patient, a defined therapeutic algorithm accepted by the FDA (Food and Drug Administration) or the EMA (European Medicines Agency) does not currently exist.

The pharmacologic therapy starts from the pathophysiological assumption that scleroderma ulcers are ischemic ulcers with endothelial dysfunction and oblitative vasculopathy with medial intimal hyperplasia complicated by endoluminal thrombotic processes and progressive destruction and impoverishment of the capillary bed and of the number of capillaries per dermal papilla until there is a desert with avascular areas. The therapeutic algorithm should therefore first of all include antiplatelet agents and vasodilators. The acquired implication of endothelial damage/dysfunction and of platelet hyper aggregability in the pathogenesis of systemic sclerosis as well as the very high prevalence of reflux esophagopathy have led experts to use, in all patients, even in the absence of digital ulcers, a basic therapy based on the association between proton pump inhibitors, acetylsalicylic acid and calcium antagonists.\textsuperscript{11}

**Antiplatelet agents**

The treatment of treating scleroderma patients with low doses of aspirin (75-100 mg/day) even in the absence of digital ulcers in virtue of the known pathophysiological mechanisms described above has become a common clinical practice. *A fortiori*, in the presence of digital ulcers it is important to administer to the patient an antithrombotic therapy with antiplatelet agents or with low
molecular weight heparin in the most significant pictures of acute ischemia.9

**Vasodilator drugs to counteract vasoconstriction and with indication for the treatment of Raynaud’s phenomenon with clinical evidence of efficacy in the treatment of scleroderma ulcers**

— Slow-release and prolonged coverage (chrono form) calcium antagonists (nifedipine), already indicated as a basic therapy in the presence of scleroderma Raynaud’s even in the absence of digital ulcers,11, 12

— Prostacyclin analogues, potent vasodilators that inhibit platelet aggregation and the proliferation of smooth muscle cells in the blood vessel wall. Iloprost is a stable prostacyclin analogue, administrable intravenously, which plays an important therapeutic role in the treatment of ischemic scleroderma ulcers as well as other pathological forms characterized by arterial hypoperfusion with consequent tissue ischemia. The therapeutic indication is the treatment of Raynaud’s phenomenon secondary to systemic sclerosis, which constitutes the most typical and precocious form of scleroderma ischemia. This therapy is therefore indicated in patients who, while being treated with the basic therapy with calcium antagonists, present repeated and prolonged asphyxic crises. Iloprost infusion therapy is the standard treatment for ischemic scleroderma digital ulcers. Iloprost has been the subject of controlled studies that have endorsed its effectiveness for the aforementioned indications. In a multicenter controlled double-blind clinical study versus placebo in patients with scleroderma Raynaud’s, the intravenous administration of iloprost for 6 hours per day for 5 days at doses of 0.5-2 ng/kg/min showed a significant reduction of digital ulcers and highlighted the persistence of effects at 9 weeks of follow-up, indicating a potential effect of the molecule of functional reset on the endothelium, and showed a potential trend of prevention of new ulcers.13 All the more so in virtue of the pleiotropic effects of iloprost on the circulatory system shown in a randomized controlled clinical trial, the infusional cyclical therapy and prolonged effect on the endothelial wall during the therapeutic interval period reinforce the potential role of the molecule in modifying the natural evolution of scleroderma vascular disease (Figures 19, 20).14

— Phosphodiesterase inhibitors: induce vasodilation by increasing the levels of bioavailability of endogenous nitric oxide (NO). The utility of using these drugs is based on the pathophysiological assumption that systemic sclerosis is a typical pathology of endothelial activation/dysfunction with imbalance between vasoconstrictor factors and vasodilator factors (including NO) in favor of the former and that tissue damage is established subsequent to this dysfunction. Raynaud’s phenomenon is the typical clinical manifestation that testifies to how the vasospasm, with consequent peripheral hypoperfusion, is one of the pathology’s typical markers. The positive effect of sildenafil and tadalafil on Raynaud’s phenomenon is shown by two randomized controlled clinical trials.15, 16 Numerous case reports and pilot studies showed efficacy of sildenafil in the treatment of scleroderma ulcers.17

**Prevention of relapse**

Scleroderma ulcers, in addition to being difficult to treat, slow healing, intensely
vascular remodeling process and the deposition of extracellular matrix. The phenomenon is driven by excessive vasoconstriction and hyperproliferation by the myocytes of the tunica media of the arteriolar component, by a proliferation of endothelial cells, and by an excessive production of profibrotic mediators by the fibroblasts, which can generate the thickening of the tunica adventitia. Endothelin-1 is also linked to an increased production of PDGF and overexpression of adhesion proteins.

From a clinical standpoint, the earliest and most common manifestation of this pathological process is Raynaud’s phenomenon and the formation of digital ulcers. By blocking the effects of ET-1, one aims to slow the progression of the vascular remodeling that underlies the ulcerative manifestations (Figure 21).

Surgical therapy

Surgical therapy is essentially reserved for extreme cases of vasospastic ischemization during the nearly continuous or subcontinuous cyanotic phase. Recourse to sympathectomy is intended to reduce the number and painful and disabling, have a natural tendency to recur.

The scleroderma patient who has already presented scleroderma ulcers, in addition to the antiplatelet and vasoactive therapy indicated above, is indicated to be treated with non-selective endothelin receptor inhibitors (Bosentan).

This indication has emerged from the results of two double-blind randomized controlled clinical trials with placebo, RAPIDS 1 and 2, that have shown the efficacy of bosentan in significantly reducing the onset of new digital ulcers in patients that are already affected by digital ulcers while the effectiveness in promoting the healing of active ulcers did not emerge. From a clinical standpoint, the earliest and most common manifestation of this pathological process is Raynaud’s phenomenon and the formation of digital ulcers.

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Surgical therapy is essentially reserved for extreme cases of vasospastic ischemization during the nearly continuous or subcontinuous cyanotic phase. Recourse to sympathectomy is intended to reduce the number and
duration of the digital asphyxiation crises and finds indication in severe digital ulcers and recurrent ulcers refractory to the combined medical therapy.

While the long-term results of cervical sympathectomy have been rather disappointing, better results are derived from digital sympathectomy associated with techniques of resection and removal of the fibrotic adventitia (microsurgical arteriolysis). This procedure has promoted healing of the lesions, and has reduced pain and the recurrence of digital ulcers.

In the case of an indication to carry out amputation procedures, common experience advises conservative procedures limited to eliminating the necrotic material, also carrying out extra-anatomic procedures aimed at the conservation of the perilesional ischemic tissue. Where this has not been carried out, driven by the natural conviction to eliminate all of the ischemic tissue in addition to the necrotic tissue to reach a resolving if demolishing solution, the result has been very disappointing, with an exacerbation of the ischemic damage of the tissue presumed healthy and further extension of the necrotizing process. Alternatively, the removal of the necrotic material and the treatment of perilesional ischemic tissue with vasoactive, antithrombotic and vasodilatory therapy allows results to be obtained that are sufficient to guarantee the recovery of a dignified relational life with conservative scarring.

Dressing of the scleroderma ulcer

A careful evaluation of the ulcer according to the principles of the TIME acronym is necessary for an optimal dressing; this acronym summarizes the essential characteristics of the ulcer by considering T (devitalized tissue), I (infection), M (maceration), and E (perilesional epithelium).

Microangiopathic ulcers in general and scleroderma ulcers in particular, in the activity phase, are extremely painful, very reactive and rather unwilling to accept aggressive local treatments of a mechanical type or surgical cleansing, which can promote an abnormal phlogistic response with a necrotizing evolution. The elimination of devitalized tissue is necessary to promote autolytic or enzymatic debridement.

Wherever signs of infection show it is important, besides systemic antibiotic treatment, to drain any local purulent collection, following delicate removal of the sclerotic cap, to obtain an immediate reduction in the pain caused by the subcutaneous collection. Bandaging should be ample at the lesion stage, with an aim of favoring the granulation stage re-epithelization.

All this requires having dedicated staff, particularly trained and knowledgeable about the disease.

Conclusions

These are difficult ulcers whose therapeutic success is contingent upon the promptness and appropriateness of the intervention. At the time of their onset, the modest sizes induce the clinician to make an optimistic and conservative wait-and-see type evaluation, given the small dimensions that are similar to a pinhole or the slit of

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**Figure 21.**—Mechanisms of endothelin’s action in vascular remodeling process.
a cut, which is absolutely the appropriate behavior for any lesion of this type in a non-scleroderma patient. Unfortunately, in many patients, the trophic lesion is the first clinical manifestation that leads the patient to medical attention before he is diagnosed with disease, with a consequent delay in the proper treatment of lesions initially approached traditionally as described above. It is exactly the rapidly worsening evolution of the lesions as well as the intense pain that is little responsive to analgesic therapies that should lead to clinical suspicion and diagnostic completion. Nevertheless, the evolution times of the scleroderma lesion are so fast that when the targeted intervention is implemented, while it often ensures the demarcation and limitation of the lesion, it does not succeed in avoiding the loss of areas of tissue already in the necrotic phase.

That said, it is evident that the optimal, economic and ideal treatment of the scleroderma ulcer starts with primary prevention, which requires the early diagnosis of scleroderma even in the early and preclinical forms when the reversible and paroxysmal phases of ischemia, represented by Raynaud’s phenomenon, manifest themselves, treating the patient with nifedipine and acetylsalicylic acid, and where prolonged and recurrent asphyxiated crises persist nevertheless, turning to the infusional cyclic treatment with iloprost. In the presence of active ulcers, the systemic treatment of the acute ischemia with an infusional therapy of iloprost, an anti-thrombotic therapy, associated with the appropriate pain management and antibiotic therapy in the case of infection, is important. In the case of recurrent ulcers, despite the optimization of the vasoactive and antithrombotic therapy, it is important to subject the patient to therapy with the non-selective endothelin-1 receptor inhibitor drug (bosentan), and, where resistant ulcers and severe Raynaud’s are present, to add the phosphodiesterase inhibitor drug (sildenafil/tadalafil). Although an antifibrotic therapy that heals systemic sclerosis is not yet available, and while ignoring if the early scleroderma syndromes will all evolve into definite systemic sclerosis, with regard to the treatment of scleroderma ulcers, the medical history evidence of the early scleroderma finding by itself puts the patient in the conditions to promptly direct the clinic, at the first appearance of the lesions, toward the most appropriate and effective therapeutic directives with less healing time, conservative outcomes, and minor impairment of the quality of life. It is, therefore, necessary, in the presence of Raynaud’s phenomenon with confirmation upon the capillaroscopy examination of the “scleroderma pattern”, that the patient carries out the diagnostic completion examinations, where possible
guided in the context of a dedicated multidisciplinary path.

The close clinical follow-up of the patient with early diagnosis allows the same a privileged and priority clinical audit at the first occurrence of any trophic lesion of any dimensions, which can be promptly treated and rapidly resolved.

Since there is no therapeutic algorithm officially accepted by the FDA for the treatment of scleroderma ulcers, the current knowledge of pathogenetic mechanisms and the results of clinical trials should guide therapeutic interventions, indicating useful principals to contrast the major known pathogenic phases of ischemic damage. Similarly to the treatment of other clinical manifestations of scleroderma vascular disease such as pulmonary hypertension, the therapeutic algorithm for the prevention and treatment of scleroderma ulcers should indicate, as described above, a combination of therapies that, starting from the earliest stages of scleroderma vascular disease, exploits the targets of activity of different molecules to have a sequential, synergistic and additive effect.

References