German S1 guideline: diagnosis and treatment of livedovasculopathy

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Overview on the strength of consensus within the expert panel

The wording and symbols listed in Table 1 were used for the standardized presentation of our recommendations.

Definition

Livedovasculopathy (LV) is a chronically recurring vascular disease with thrombi in the microcirculation that result in impaired skin perfusion and ulceration. These ulcerations occur only on the lower limbs, especially the malleolar region.
Synonyms
Various other terms have also been used to describe LV: Livedo reticularis with summer ulceration, hyalinizing vasculitis, PPURPLE (painful purpuric ulcers with reticular pattern of lower extremities), livedovasculitis; idiopathic atrophie blanche.

In ICD-10 code, the disease is registered as L95.0 livedovasculitis including capillaritis alba.

Endothelial proliferation with vascular occlusions was first described in the 1950s [1]. The authors were the first to report on the appearance of new, painful ulcerations during summer, so-called summer ulcerations. These were associated with livedo patterns. The term hyalinizing vasculitis [2] was used based on the histological findings. However, “vasculitis” incorrectly suggests an inflammatory pathomechanism. This also applies to the term livedovasculitis, since the disease is not primarily a vasculitis (vascular inflammation) [3].

English-language publications use the term painful purpuric ulcers with reticular pattern of lower extremities (PPURPLE), which emphasizes the lower limbs as predilection sites [4]. Scarring leads to atrophie blanche: porcelain-colored scars resembling a lightning pattern or a star. Capillaritis alba is used synonymously [5].

Epidemiology
The disease is more common in women than in men, with a reported sex ratio of 2.1 : 1 [6, 7] or 3 : 1 [8]. Our expert panel assumes a female-to-male ratio of 3 : 1.

There are hardly any data on the incidence of LV. From their own experience, Fritsch et al. assume an incidence of 1 : 100,000 persons per year [9]. Reports on median age at the time of first diagnosis vary between 32 and 53 [10]. However, cases with younger female patients have also been described [11]. Increased body mass index (BMI) as well as arterial hypertension have been described as co-factors. To date, no specific comorbidities associated with a higher incidence of LV have been identified.

Pathogenesis
The pathomechanisms of livedovasculopathy remain unclear. However, it has been established that in the fine-tuning of hemostasis, a preponderance of procoagulatory factors leads to thrombus formation in the microcirculation of the upper and middle dermis, with consecutive cutaneous ischemia (skin infarction) [12].

Various procoagulatory factors have been described for LV. These include impaired endothelial plasminogen activation, impairment of platelet function, and increased fibrin formation. Fibrin deposits and thrombus formation lead to tissue ischemia and subsequent ulceration. Decreased perfusion also results in impaired wound healing and trans-endothelial leukocyte migration – which in turn promotes wound infection [13–15]. Patients with LV show an increased incidence of anticardiolipin antibodies and lupus anticoagulant, increased levels of plasminogen activator inhibitor (PAI-1-4G/SG polymorphism), and decreased activity of tissue-type plasminogen activator, t-PA [16]. Thrombophilia can additionally be promoted by antithrombin III deficiency, protein-C deficiency, or protein-S deficiency. Associations with prothrombin-G20210A mutation, cryoglobulins, or factor-V Leiden mutation are rare [6, 17, 18]. Methylene tetrahydrofolate reductase deficiency leads to impairment of homocysteine metabolism, which also increases thrombophilia [19, 20].
Increased levels of lipoprotein(a) are an additional pro-coagulatory parameter in LV diagnostics. Lipoprotein(a) is structurally similar to plasminogen and thus has anti-fibrinolytic properties, increasing thrombophilia. Increased lipoprotein(a) levels thus also constitute a cardiovascular risk factor [11, 21, 22].

Although there is now consensus that LV is a disorder of coagulation, extensive studies with large patient populations have shown that pathological changes of known pro-coagulatory factors can be found in less than 50% of cases [23]. Conversely, occurrence of one of the abovementioned anomalies is not consistently associated with LV.

The predilection site is also of pathogenetic relevance. The high perfusion pressure and low temperature of the lower limbs result in a low concentration of thrombolytic factors. This increases thrombophilia [24].

No statistical association with malignomas has been observed. However, secondary LV-like lesions may occur in patients with autoimmune diseases or malignomas, which requires causal treatment and further diagnostics [11, 25].

| Recommendation 2 |
|------------------|
| – In LV patients, coagulation diagnostics with screening for pro-coagulatory parameters is recommended. (EC -1.6) (see also Recommendation 5) |
| – LV may be diagnosed even without evidence of pro-coagulatory factors (EC +1.9) |

Clinical appearance and course of disease

The disease progresses in three typically recurrent stages, which may thus appear simultaneously in the same patient. In the first stage, depending on individual disposition, livedo racemosa markings will appear. These are characterized by livid, irregularly circumscribed, reticular macules. The macules are caused by impaired perfusion of the dermal stratum reticulare. The net-like pattern results from cross-segment perfusion, with the vessels bordering on the area with impaired perfusion providing compensating supply except for some residual zones. Livedo racemosa must be differentiated from livedo reticularis, a functional condition caused by hypoxia and slowed blood flow. Clinically, this is characterized by regular and closed livid rings, for example after exposure to cold. During the second stage of LV, impaired perfusion leads to tissue ischemia. New ulcerations are typically preceded by burning pain limited to the affected region (manifestation site). This highly localized pain occurs in the prodromal phase of the disease and is also called angina cutis [12]. There is usually an interval of 1–3 days between angina cutis (the prodromal phase) and the occurrence of necroses. Tissue necrosis can often still be prevented by rapid initiation of therapy during this period. If the prodromal phase passes without treatment, ischemic necrolysis of the epidermis will result in necrosis and sometimes hemorrhagic blisters. Ulceration with crusts will ensue. Atrophie blanche, a lightning-shaped or star-like porcelain-colored scar, is the sign of chronic disease with scar-forming remodeling processes.

As described above, the classical clinical presentation shows the triad of livedo racemosa, ulceration with severe pain, and atrophie blanche. Depending on the individual course of the disease, the clinical signs may occur separately or in combination. None of the cardinal symptoms is pathognomonic for LV. The disease is chronic; phases of healing may coincide with new relapses. Neurological affection has also been reported, characterized by dysesthesia and hypesthesia. Symptoms may vary with the season, with some patients experiencing deterioration during the summer months.

It should, however, be stressed that LV may occur year-round. In contrast to the synonymously used term “summer ulceration” (see above), LV may appear at any time. Diagnosis is not limited to symptoms occurring in summer. Both seasonal clusters and year-round symptoms have been described.

LV is limited to the lower limbs, in particular the malleolar region. The disease typically does not appear above the knees [6].

Quality of life is significantly impaired by LV. The Dermatology Life Quality Index (DLQI) is important both for diagnosis and monitoring of the disease, and it should also be taken into consideration for decisions on treatment changes. The DLQI incorporates values up to 30, but anything above DLQI 10 already indicates severe impairment of the patient’s quality of life. LV patients report severe impairment of their quality of life, with DLQI values up to 17.8 [23, 26, 27]. In patients with ulceration, the Wound-QoL score [28] can be used to gain additional information on quality of life.

| Recommendation 3 |
|------------------|
| The following clinical aspects should be taken into consideration for diagnosis: |
| – Painful, recurrent ulcerations (EC +1.9) |
| – Triad: Livedo racemosa, ulceration, atrophie blanche (EC +1.9) |
| – LV may occur year-round. (EC +1.7) |
| – LV is more common in women than in men. (EC +1.6) |
| – New ulcerations are typically preceded by burning pain limited to the affected region (manifestation site). (EC +1.6) |
Diagnostics

LV is diagnosed from the combination of typical clinical signs and histology. A medical history of burning pain strictly localized to the manifestation site (angina cutis), which may occur at any time during the year, is a leading symptom. According to the literature, the interval between the first symptoms and the diagnosis ranges from four months to more than seven years [6]. Thus many patients will show advanced scarring of the skin in the affected area. Early treatment, and therefore prevention of irreversible scarring, is the therapeutic goal. The various criteria for diagnosis are summarized in Table 2.

Histology

Histological confirmation of the diagnosis is only possible during the acute (ischemic) stage of the disease. A sufficiently large specimen (if possible, a spindle biopsy) should be taken from the margin of the affected area. Fibrin deposits in the vascular walls are characteristic but often difficult to detect, and fibrin thrombi can be found mainly in the vessels of the upper and middle dermis. Perivascular inflammatory infiltrations and leukocytoclasia are not typical for this disease and are only discreet during the acute phase if present at all. Prominent inflammatory affection of the vessel walls, or (fibrinoid) vessel wall necrosis, are more indicative of primary vasculitis. If specimens are taken at later stages, secondary inflammatory infiltration may be present [12]. The stage of atrophie blanche is characterized by scarring with few vessels and atrophic epidermis. Thrombus re-organization with subintimal proliferation and segmental hyalinization of the vessel walls and dermis may also occur [9].

Immunfluorescence is non-specific. Detection of immunoglobulins or complement deposits is a non-specific reaction without any pathogenetic relevance. It has no significance for the diagnosis [12].

Recommendation 4

The following histological criteria should be noted:
- Intraluminal thrombi in the upper and middle dermis (EC +2)
- No primary inflammation as in vasculitis (EC +1.8)
- Subintimal hyaline deposits (EC +1.6)
- Endothelial proliferation (EC +0.9)

Laboratory parameters

Various prothrombotic parameters are frequently associated with LV (Tabelle 3). These include both parameters for hypercoagulation and parameters for impaired fibrinolysis. Simultaneous occurrence of several parameters may increase the risk of manifestation above the simple addition of risks [20]. Due to the high cost, it is recommended to consult specialized centers for assessing prothrombotic parameters. However, even if such parameters are detected the diagnosis of LV requires the combination of clinical appearance and histology [12]. Laboratory changes are not pathognomonic. Cryoglobulins should be assessed if hepatitis C has been detected [31]. For thrombophilia diagnostics, please refer to the S2 guideline “Diagnosic

Table 2  Diagnostic criteria (modified according to [6]). A score for reliable diagnosis is currently not validated.

| Main criteria | Additional criteria |
|---------------|---------------------|
| – Ulceration (malleolar region, backs of the feet, lower legs) | Prothrombotic parameters |
| – Angina cutis (localized stinging or burning pain) | Common (in LV): |
| – Atrophie blanche | – Increase of lipoprotein(a) |
| – Livedo racemosa | – Increase of antithrombin-III |
| – Intraluminal fibrin thrombi | – Hyperhomocysteinemia |
| – subintimal hyaline deposits | Rare (in LV): |
| – no primary inflammatory changes | – Factor V mutation |
| – endothelial proliferation | – Prothrombin-G20210A mutation |
| Histology: | – Plasminogen activator inhibitor deficiency |
| – Intraluminal fibrin thrombi | – Protein C and protein S deficiency |
| – subintimal hyaline deposits | – Comorbidities |
| – no primary inflammatory changes | – (BMI > 25 kg/m², hypertension) |
| – endothelial proliferation | – Female |
| | – Therapeutic response to anticoagulation |
| | – Both legs affected |
Procoagulatory factors were detected in < 50 % of large patient cohorts [6]. If procoagulatory parameters are detected, this is called secondary LV, while LV without evidence of procoagulatory factors is called primary LV. In some cases, extended diagnostics with the involvement of a hemostaseologist may be helpful.

**Recommendation 5**

Initial laboratory diagnostics should include the following parameters:
- Antiphospholipid antibodies (EC +1.7) (Lupus anticoagulant, antiphospholipid antibodies, β2 glycoprotein-1 antibodies)
- Protein C (EC +1.3)
- Protein S (EC +1.3)
- Homocystein (fasting) (EC +1.2)
- Lipoprotein(a) (EC +1.1)

**Differential diagnoses (Table 4)**

LV can be differentiated from other diseases with lower limb ulcers mostly by its typical clinical appearance (stinging pain, year-round occurrence) and its characteristic histology during the early stages.

The two most important differential diagnoses are caused by degenerative vessel disease: arterial leg ulcers in peripheral arterial occlusive disease (PAOD), and venous leg ulcers in chronic venous insufficiency (CVI).

Patients with PAOD frequently present with lesions on the legs (mainly the lower legs) that resemble LV: simultaneous occurrence of livedo-racemosa-like erythema, painful ulcers, and atrophie blanche. On the other hand, PAOD usually occurs in older patients than LV, it is frequently associated with medical comorbidities, and angiological diagnostics with assessment of arterial occlusive pressures will reveal the diagnosis.

Venous leg ulcers usually develop more slowly. Duplex sonography shows a reflux, and other typical findings include dermatoliposclerosis, yellowish-brown hyperpigmentation (purpura jaune d’ocre), visible varicosis [32], and paraplantar corona phlebectatica.

Cutaneous polyarteritis nodosa (PAN) is another possible differential diagnosis, with the shared symptom of livedo racemosa. Palpable subcutaneous nodules usually precede ulceration. Dysesthesia (multiple mononeuritis) may also be present in the affected limb. Internal organs are not affected by cutaneous PAN. Treatment with glucocorticoids usually produces a good initial response [33]. Histology shows vasculitis of medium-sized
vessels/arterioles in the border area between the subcutis and the dermis – a lower level than the vessel involvement in LV [34].

In contrast to pyoderma gangrenosum, LV lacks the undermined livid margin [9]. Other differential criteria include locality (70% on the extensor sides on the lower legs), rapid growth, and the pathergy phenomenon. Pyoderma gangrenosum may occur anywhere on the body while LV is limited to the lower legs. It also responds very well to systemic glucocorticoids or ciclosporin [35].

Additional differential diagnoses are cutaneous manifestations of vasculitis [36] and vasculitis associated with cryoglobulinemia [37, 38].

Secondary LV-like lesions may appear in patients with autoimmune disease or malignomas; this requires causal treatment and additional diagnostics [11].

Occlusive vasculopathies such as the one associated with cryoglobulinemia type I must also be differentiated from LV [37].

**Treatment**

Early initiation of medical treatment is essential to prevent progression of chronically recurring skin infarctions with scarring at the manifestation site.

Raised awareness of the disease, and inclusion of LV in the differential diagnosis, should reduce the time lag between the first clinical symptoms and the correct diagnosis.

**Ranking of treatment recommendations according to expert consensus (EC) (Table 5)**

**Treatment algorithm in first-line anticoagulation (Figure 1)**

**Low-molecular-weight heparin**

Treatment with low-molecular-weight heparin (LMWH) usually achieves rapid success [6]. A semi-therapeutic dose is recommended as maintenance therapy (for example enoxaparin 1 mg per kg body weight [BW] once a day subcutaneously (off label)). Clinical deterioration of ulcerations is usually preceded by a period of intensifying pain. Pain diaries are very helpful in detecting deterioration [12, 39]. If the pain increases, dosage should also be increased. Exacerbations require the full therapeutic dose (in the case of enoxaparin, 1 mg/kg BW subcutaneously twice a day in the morning and evening (off label)). The time lag between initiation of treatment or increasing the dose and the resulting pain relief is 2–4 days, so the therapeutic response can be assessed rapidly. Possible side effects of heparin treatment include heparin-induced thrombocytopenia (HIT). Checking the platelet count twice a week during the first four weeks of treatment may be helpful. Severe renal failure (creatinine clearance 15–30 ml/min) requires lower doses since the risk of bleeding complications may otherwise be increased. Regular monitoring of laboratory values must be performed since hepatic parameters may rise. The risk of osteoporosis is low [40]. Low-molecular-weight heparin can also be used to treat LV in children (off label) [11, 41].

**Recommendation 6**

- Clinical deterioration of ulcers is usually preceded by a period of intensifying pain. Increasing the dose of anticoagulants should therefore immediately be considered upon marked worsening of the pain. (EC +1.9)
- A diary can help to monitor pain. (EC +1.9)
- Treatment with low-molecular-weight heparin should be initiated at the full therapeutic dose (for example enoxaparin 1 mg/kg BW subcutaneously twice a day in the morning and evening (off label)) (EC +1.4)
- Once findings are stable, dosage should be reduced to a semi-therapeutic level (for example enoxaparin 1 mg/kg BW subcutaneously once a day (off label)) (EC +1.3)

**Direct oral anticoagulants (DOAC)**

Direct oral anticoagulants or DOAC include the Factor-Xa inhibitors – rivaroxaban (Xarelto®), apixaban (Eliquis®),

| First line EC +2 to +1 | Second line EC +0.9 to 0 | No clear recommendation in the view of the guideline authors EC –0.1 to –2 |
|------------------------|--------------------------|-------------------------------------------------------------------------|
| 1. Low-molecular-weight heparin | – Phenprocoumon/ Warfarin | – NSAID |
| 2. Rivaroxaban/DOAC | – Iloprost | – Glucocorticoids |
| 3. Intravenous immunoglobulins (IVIG)* | – Vitamin B6, B12, and folic acid (in cases of hyperhomocysteinemia) | – Fibrinolytics |
| | | – Hyperbaric oxygen treatment |
| | | – PUVA |
| | | – Danazol |
| | | – Leeches |

*For cost-effectiveness, prioritize other first-line therapies despite good efficacy of IVIG.
and edoxaban (Lixiana®) – as well as the thrombin inhibitor dabigatran (Pradaxa®) [42, 43]. Rivaroxaban offers the most comprehensive database on the treatment of LV. Studies have been performed with 10 mg rivaroxaban once a day for maintenance, and 10 mg twice a day in cases of exacerbation or recurrence. Rapid pain relief was observed in these cases [23]. The oral administration and non-requirement for monitoring of laboratory parameters is a clear advantage and has been shown to result in better patient adherence [10].

There have also been individual case reports on the successful use of apixaban (10 mg/day), edoxaban (15–60 mg/day), or dabigatran (220 mg/day) for treating LV [42–44]. If antiphospholipid antibodies are present, DOAC should not be used since treatment with rivaroxaban in patients with antiphospholipid syndrome has been shown to increase the risk of recurring thrombotic events [45].

**Recommendation 7**

- DOAC have the advantage of oral over subcutaneous application, resulting in improved compliance/adherence. (EC +2)
- Switching from LMWH treatment to rivaroxaban up to 15 mg twice a day is possible (off label). (EC +1.8)
- Subsequently, rivaroxaban can be administered at 20 mg once a day (off label). (EC +1.9)
- If findings remain stable, the dose can be reduced to 10 mg/day (off label). (EC +1.9)

**Intravenous immunoglobulins (IVIG)**

Intravenous immunoglobulins (IVIG) constitute an effective therapeutic intervention. The authors recommend a dose of 2 g/kg BW (off label). To increase tolerability, the dose may be split and administered over a period of 2–5 days.

Monsi et al. reported significant pain relief and an increase in DLQI after only six treatment cycles [26]. Case series indicate a good therapeutic response, especially for treatment-refractory ulcers [46–48].

The precise mechanism of action is still unknown. IVIG modulate cytokine production, they neutralize pathogens and inhibit complement-mediated tissue damage [49]. Note that this type of treatment is expensive. Side effects mainly include allergic rash and headaches.

**Recommendation 8**

- The attending physician must decide if IVIG is indicated, independently of previous treatments. (EC +1.9)
- IVIG treatment is recommended in treatment-refractory LV (off label). (EC +1.6)
- The authors recommend a dose of 2 g/kg BW which may be split into several doses and administered over a period of 2–5 days (off label). (EC +1.6)

**Phenprocoumon and warfarin**

Phenprocoumon (such as Marcumar) and warfarin (such as Coumadin) inhibit vitamin K dependent coagulation factors as well as the anticoagulant proteins C and S which are relevant for micro-circulation. The therapeutic range is between INR 2.5 and 3.5. In cases of protein C or protein S deficiency, treatment initiation must be complemented with additional heparin. This is due to the shorter half-life of the anticoagulant proteins C and S as compared to the pro-coagulant factors (II, VII, IX...).
and X), which results in a prothrombotic state and markedly increases the risk of coumarin necroses shortly after treatment initiation, especially in cases of pre-existing deficiency of protein C and S [50]. Since there are new, safer alternatives, and due to the reduction of protein C and S concentrations, coumarin derivatives should now be limited to exceptional cases such as antiphospholipid syndrome (off label).

**Iloprost**

Case reports have shown good results in ulcer healing with iloprost. The recommended dosage is 1–2 ng iloprost/kg BW/min i.v. over a period of six hours per day at intervals of 1–4 weeks [51]. There have also been reports of infusion therapy once or twice a week over a period of five days for cases with recurring pain [52].

**Recommendation 9**

- Complementary treatment or monotherapy with iloprost may be considered in treatment-refractory LV (off label). (EC +0.1)

**Glucocorticoids**

As opposed to vasculitis, LV is not caused by primary inflammation but by an increased pro-coagulatory state. Therefore, glucocorticoids do not offer a direct therapeutic benefit for LV. They are only relevant in cases of associated autoimmune disease for treating the underlying disorder. There has been one case report on Sjögren’s syndrome [53] and on the association with lupus erythematosus [54].

**Recommendation 10**

- In cases of associated autoimmune disease, glucocorticoids should be used for treating the underlying disorder. (EC +1)

**Folic acid and vitamin B12 in cases of hyperhomocysteinemia**

Any underlying diseases or pro-coagulatory disorders should, if possible, be treated in a targeted manner. Methylene tetrahydrofolate reductase deficiency leads to impairment of the homocysteine metabolism and to hyperhomocysteinemia. Studies show that in these cases, administration of vitamins B6 and B12 as well as folic acid, which help normalize homocysteine levels, is beneficial when combined with anticoagulants [20, 55, 56].

**Recommendation 11**

- Patients with hyperhomocysteinemia should receive additional treatment with the vitamins B6, B12, and folic acid (off label). (EC +1.4)

**Non-steroidal anti-inflammatory drugs (NSAID)**

No causal beneficial effect has as yet been reported for NSAID [6]. Administration of NSAID may, however, be considered for supportive pain relief [57].

**Hyperbaric oxygen therapy**

There are individual case reports on successful treatment with hyperbaric oxygen. Patients received five 90-minute sessions per week over a period of 2–5 weeks. During therapy, pain was reduced after one week, and healing of active ulcers was observed after 3–4 weeks. Some relapses occurred after about six months [58]. In summary, hyperbaric oxygen therapy is time-consuming and expensive, but rapid pain relief and clinical improvement were achieved [59]. Available reports also show that therapeutic success was short-lived in some cases [58, 60].

**Supportive Measures**

If the patient can tolerate it, class I compression therapy (corresponding to 20 mmHg) may be considered. In addition, an attempt to avoid large temperature fluctuations can be made, because they counteract an even perfusion. Presentation to a center with appropriate experience in the treatment of LV is recommended.

**Wound care and pain relief**

Treatment of pain should be performed in accordance with the WHO Analgesic Ladder. The S3 guideline on wound care (DGfW 2014, https://www.awmf.org/leitlinien/detail/ll/091-001.html) should also be adhered to. In the rare event of bacterial superinfection, appropriate antibiotic treatment is recommended.

**Other treatments**

In cases of treatment-refractory ulcerations, treatment with tissue-type plasminogen activator (t-PA), which activates fibrinolysis, may be considered. A recombinant version (alteplase) is utilized for therapeutic purposes. LV can be treated with 10 mg alteplase per day (off label). This is about ten percent of the dose used for myocardial infarction or pulmonary embolism [10, 61]. Therapeutic success has been reported with intravenous administration for four hours per day, over 14 days [16].

Pentoxifyllin stimulates prostacyclin synthesis, reduces platelet aggregation, and increases fibrinolysis as well as the motility of neutrophils. In some older reports in the literature, a positive effect of pentoxifyllin 400 mg three times a
day for LV was claimed [62–64]. More recent studies, however, have failed to demonstrate any effect of pentoxifyllin monotherapy [65].

There are individual case reports of successful treatment of LV with systemic PUVA with 8-methoxypsoralen (8-MOP) [66, 67]. These authors discuss a possible immunological mechanism of action.

Danazol is a synthetic anabolic steroid. As a testosterone derivative, it has androgenic properties. In addition, fibrinolytic properties and the ability to reduce lipoprotein(a) levels in the serum have also been described. For LV treatment, studies have used 3–5 mg/kg danazol or 200 mg danazol per day [68]. Treatment response was observed after 1–2 weeks [69]. The correlation of the therapeutic response with the decrease of lipoprotein(a) levels was particularly striking. Note that due to the androgenic properties and corresponding side effects, administration of danazol in young women requires careful consideration.

Independently of any previous treatments, the attending physician should decide on the indication for a therapeutic option. Depending on the severity and characteristics of symptoms, it may be necessary in individual cases to omit some of the abovementioned therapeutic steps to ensure the best possible individual treatment plan for the patient.

**Conclusion and outlook**

Awareness of LV as a clinical entity has been increasing in the last few years. Our expert consensus has revealed that the ‘classic’ summer ulcerations only affect a small percentage of patients and that the disease may occur at any time during the year.

Further research is needed, particularly with regard to LV-associated prothrombotic factors and molecular pathomechanisms. Simultaneous occurrence of multiple factors may further increase the risk of manifestation beyond mere addition. Laboratory changes, however, are not pathognomonic.

Low-molecular-weight heparin (LMWH) and DOAC (such as rivaroxaban) should be emphasized as first-line treatment choices (off label). IVIG are another important therapeutic option (off label). Therapy with IVIG should routinely be made available to patients who have not responded sufficiently to previous treatments.

Since LV is a chronic disease, the therapeutic goal is long-term improvement and maintenance of patients’ quality of life.

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**Conflict of interest**

None.

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