Controversies in the diagnosis and treatment of deep vein thrombosis for vascular ultrasound

Controvérsias no diagnóstico e tratamento da trombose venosa profunda pela ecografia vascular

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Abstract

Deep vein thrombosis is a potentially serious clinical entity, responsible for high morbidity and mortality. The vascular ultrasound is the diagnostic methods of choice in the diagnosis and monitoring of patients with this disease. However, several issues remain controversial, such as the initial approach of patients with suspected deep vein thrombosis, protocols to be used, the time for the exam and thrombosis in the calf plexus. The objective of this review is to discuss these issues in light of current knowledge.

Keywords: venous thrombosis; ultrasonography, Doppler, color; diagnostic techniques, cardiovascular.

Resumo

A trombose venosa profunda é uma entidade clínica potencialmente grave, responsável por elevada morbimortalidade. A ecografia vascular representa o método propedêutico de escolha no diagnóstico e acompanhamento dos pacientes com essa doença. Entretanto, várias questões permanecem controversas, tais como a abordagem inicial do paciente com suspeita de trombose venosa profunda, os tipos de protocolo a serem usados, o tempo para a realização do exame e a trombose no plexo de panturrilha. O objetivo dessa revisão é discutir esses assuntos à luz dos conhecimentos atuais.

Palavras-chave: trombose venosa; ultrassonografia Doppler em cores; técnicas de diagnóstico cardiovascular.

Introduction

Deep vein thrombosis (DVT) is a severe clinical entity characterized by the formation of thrombi in deep veins, notably in the lower limbs (80-95% of cases). DVT is the third leading cause of cardiovascular disease in the US, with approximately 200 thousand new cases per year[1]. In Brazil, the incidence is around 0.6 per 1,000 inhabitants/year. Three main factors are directly related to the genesis of thrombi: blood stasis, endothelial injury and hypercoagulability. Among the major complications, we can mention chronic venous insufficiency (post-phlebitic syndrome) due to injury of the venous valves leading to venous reflux, and pulmonary embolism, which presents a high mortality rate, most cases occurring among hospitalized patients, even though it could be avoided with prophylactic measures such as the use of anticoagulants[2].

Since Talbot[3], in 1983, first diagnosed thrombi in the subclavian vein of a patient complaining of sudden pain and swelling in the arm using high-resolution ultrasonography imaging, vascular echography became the method of choice for the diagnosis and follow-up of patients with DVT. The sensitivity and specificity of this method compared to investigations with flebography is about 96%[4].

However, several issues regarding the use of vascular ultrasound in the diagnosis of DVT remain controversial, such as the protocol to be used, the time for exam performance, and calf plexus thrombosis. The aim of this literature review is to bring about a discussion on these issues based on current knowledge.

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Deep vein thrombosis diagnosis at emergency

Facing a patient with suspected DVT, many questions are raised: what is the best diagnostic strategy? What is the most appropriate time to perform diagnosis? Should I start treatment right away?

Although DVT cause few specific symptoms, well-directed anamnesis and physical examination are essential in the initial management of patients with findings that may suggest DVT. Knowing the main factors related to the thrombotic process genesis, such as previous surgery, immobilization for more than three days, neoplasms and hormone therapy with estrogen associated with pain and unilateral limb edema are strongly related to DVT and can be classified according to clinical prediction models[5]. Wells et al. developed a model of patient classification based on signs and symptoms, risk factors and alternative diagnoses, thus estimating a pretest probability as low, medium and high-risk for DVT (Table 1). This classification has been proved useful in the initial management of patients[6,7].

Once clinical findings not always correlate with pathological changes (clinical diagnosis is correct only in 50% of cases) and, as undiagnosed DVT can lead to fatal pulmonary embolism, an totally preventable condition when the appropriate treatment is established in time, complementary exams and specific vascular propedeutics is recommended to confirm or exclude this diagnosis[8,9].

Dosage of D-dimer is one of the tests used for initial evaluation of patients with suspected DVT and is used in any situation with fibrin formation and degradation; therefore, it is not a specific marker. D-dimer negative predictive value is 94-95%[10], which indicates an incidence of DVT of 5-6% after the test, which is not sensitive enough to exclude the hypothesis of deep venous thrombosis[11]. Studies have established two main features in the diagnosis of venous thromboembolism: the need to combine D-dimer determination with pretest clinical probability score before proceeding with the diagnostic investigation.

These tests combined will reduce the incidence of DVT after the test to less than 0.5% and the need for ultrasonography to 40-50%[12].

Several studies have suggested that consecutive assessments of clinical score, D-dimer test and vascular ultrasound bring better results when it comes to the cost-effectiveness of DVT diagnosis, and are related to a significant reduction of ultrasound requests and increase in time for the patient and the physician

In patients with low risk for DVT, negative D-dimer score is related to a negative predictive value to reducing the need for other imaging examinations, and the use of clinical criteria associated with D-dimer score has a good cost-effectiveness value.

But how long can we wait to perform vascular ultrasound examination? The clinical suspicion of thrombosis represents a major impact for the patient and demands immediate investigation. In Brazil, only physicians can perform ultrasonography and the 24-hour shifts of health professionals represent a challenge for hospital costs management. Some studies, however, have shown protocols that enable proper diagnosis that do not demand the professional to work out of their shift[13,14].

Based on these studies and diagnostic guidelines[15-17], we have been using a protocol that enables an efficient diagnostic method without therapeutic loss (Figures 1-4):

- outpatients with low risk for DVT and negative D-dimer. These factors have a high negative predictive value when associated. Thus, there is no need for imaging tests to exclude DVT (Figure 1); patients with moderate to high probability require imaging studies (such as vascular ultrasound, in cases of suspected cavo-iliac thrombosis, CT angiography or magnetic resonance angiography) (Figures 2 and 3); hospitalized patients require imaging studies (such as vascular ultrasound in cases of suspected cavo-iliac thrombosis, CT angiography or magnetic resonance angiography) for diagnosis (Figure 4).

Table 1. Wells' criteria for the diagnosis of deep vein thrombosis.

Ongoing neoplasms (under treatment in the last 6 months): 1 point
Palsy, paresia or recent imobilization of lower limbs: 1 point
Recent need for prescribed rest for mor than 3 days OR major surgery that required general raquidian anesthesia or in the last 12 weeks: 1 point
Pain at palpation of the deep venous path of lower limbs: 1 point
Whole limb swelling: 1 point
Bigger Cacifo sign on the affected limb: 1 point
Swelling of the affected calf, with 3 cm of difference compared to the contralateral limb (measure 10 cm below tibial tuberosity): 1 point
Superfitial collateral veins (non varicose): 1 point
More likely differential diagnosis:<2 points

Source: modified from Rollo et al.[17].
Risk interpretation score: 0 points – low; 1 to 2 points – moderate; >2 points – high.

Protocols

Different protocols have been proposed for the ultrasonographic evaluation in DVT diagnosis: assessing all

venous segments of the lower limb, as well as the entire proximal (femoropopliteal) segment, and even the two-point evaluation (common femoral and popliteal veins).

Ultrasonography with two-points compression for DVT investigation on the lower limbs, performed by physicians in the emergency room were proven accurate for the identification thrombosis[18,19]. A randomized study published in 2008 showed that both diagnostic strategies (conventional and two-point protocol) were equivalent when used for the management of symptomatic outpatients with suspicion of DVT of the lower limbs in relation to the incidence of venous thromboembolism (VTE) after three months of follow-up[20].

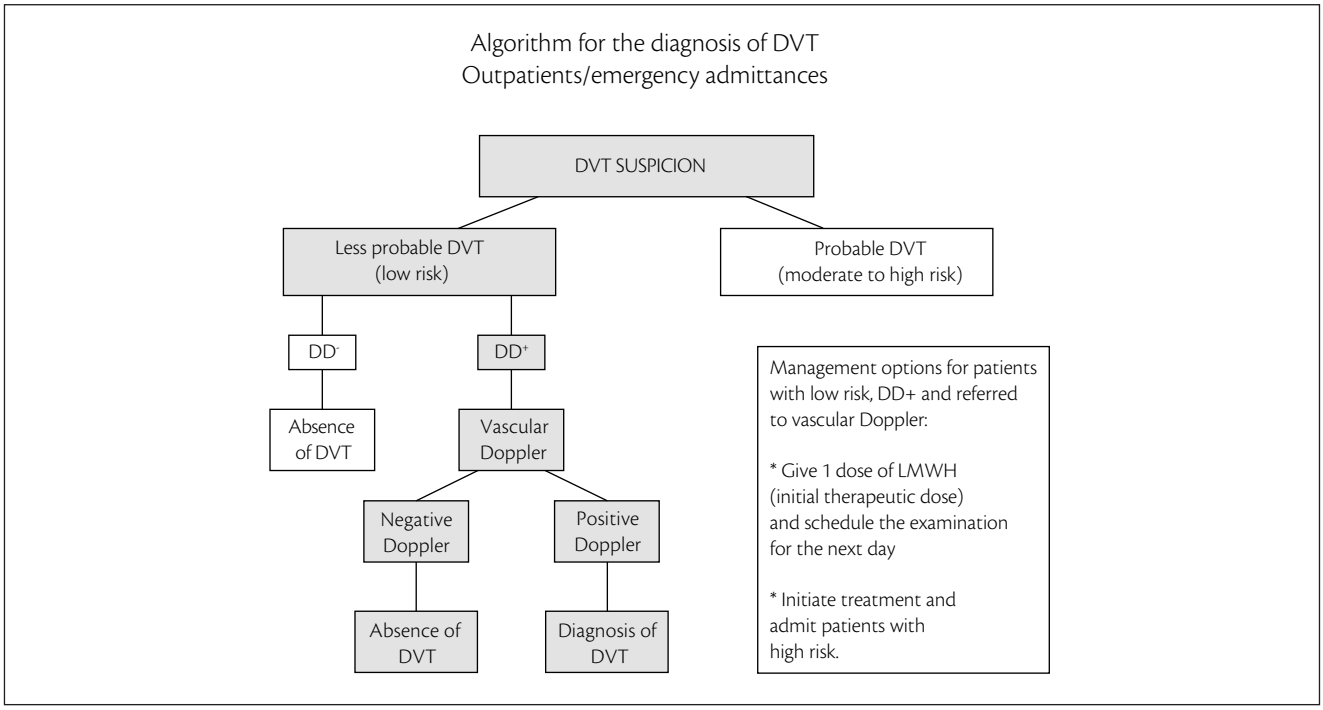
Although several protocols which address the proximal segment only have shown excellent short-term prognosis, we believe that evaluating the whole venous system is essential to the adequate approach, for, although an infrapopliteal DVT cannot determine unfavorable short-term outcomes, proper diagnosis is extremely important for the patient, as a matter of secondary prevention approach facing a recurrence. Furthermore, examining the infrapopliteal segment allows diagnosis of other pathologies such as Baker's cyst, hematomas, and muscle ruptures.

Should deep vein thrombosis investigation be bilateral?

The evaluation of bilateral DVT in patients with symptoms in only one of the lower limbs is a controversial issue.

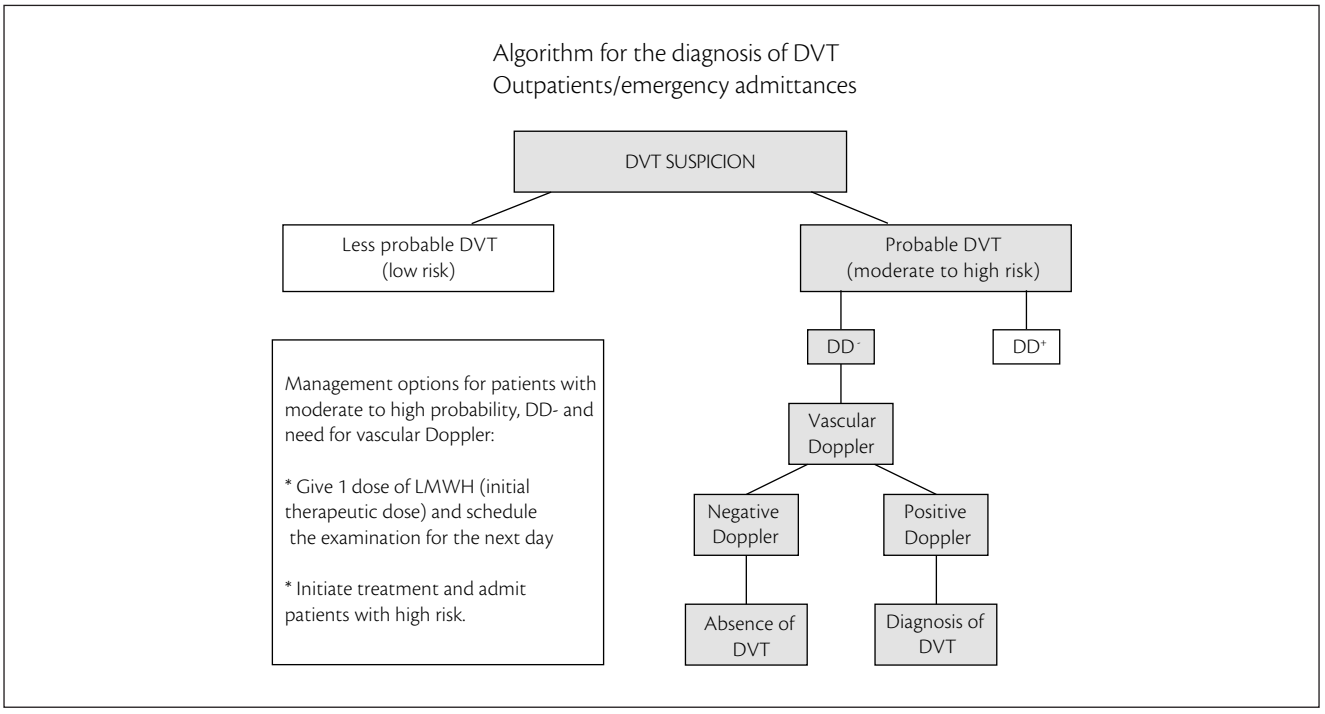
Garcia et al. found no signs of DVT in the asymptomatic limbs of outpatients with unilateral symptoms at vascular ultrasound, so the investigation of the symptomatic limb was enough to diagnosis. However, inpatients with unilateral symptoms were diagnosed with thrombosis on the symptomatic side in 24% of cases, on the asymptomatic limb in only 5%, and on both limbs in 5% of cases[21]. In another study, Lemech et al. found about 10% of bilateral DVT in patients with unilateral symptoms, thus suggesting that inpatients should have both limbs investigated[22].

Pennell et al. showed that inpatients have a high incidence of clinically silent contralateral thrombosis (34%) and usually must undergo bilateral examination, as well as patients with malignant disease, whose incidence of asymptomatic blood clots is 38%. Outpatients with unilateral symptoms and without risk factors for thrombosis should undergo unilateral examination and be treated properly according to the results. Algorithms to select patients for unilateral studies should include



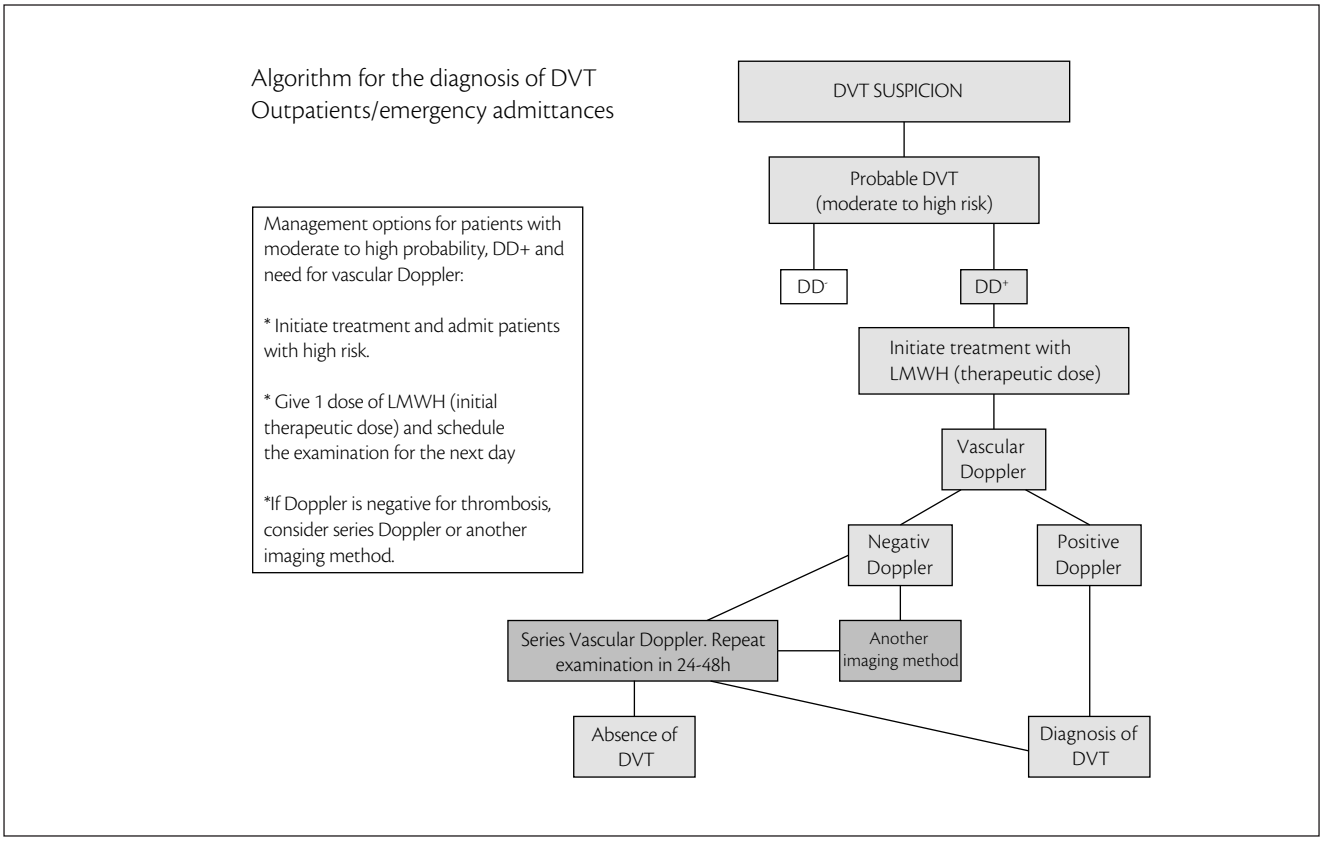
DVT - deep vein thrombosis; DD - negative D-dimer; DD+ - positive D-dimer; LMWH - low-molecular-weight heparin.

Figure 1. Algorithm for the diagnosis of deep vein thrombosis for outpatients or emergency admittances – low risk of DVT.



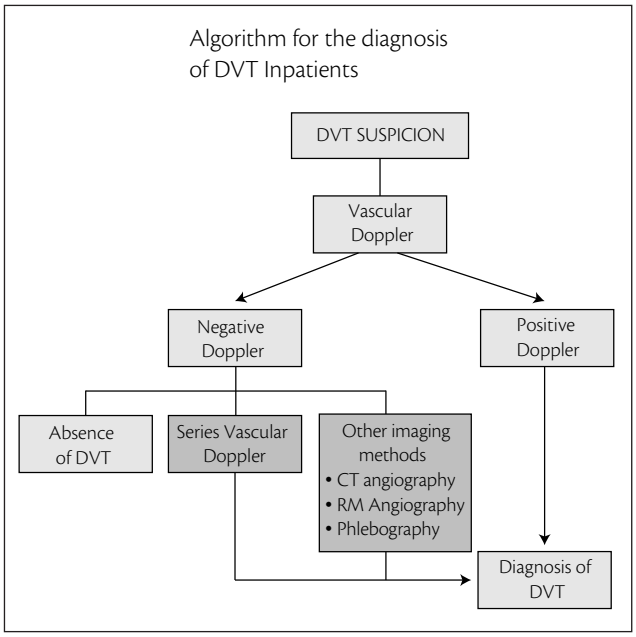
DVT - deep vein thrombosis; DD - negative D-dimer; DD+ - positive D-dimer.

Figure 2. Algorithm for the diagnosis of deep vein thrombosis for outpatients or emergency admittances – moderate to high risk of DVT and DD-.



DVT - deep vein thrombosis; DD - negative D-dimer; DD+ - positive D-dimer.

Figure 3. Algorithm for the diagnosis of deep vein thrombosis for outpatients or emergency admittances – moderate to high risk of DVT and DD+.



DVT - deep vein thrombosis.

Figure 4. Algorithm for the diagnosis of deep vein thrombosis for inpatients.

data from active malignant diseases, recent trauma or surgery, pregnancy, hormone therapy or history of thrombophilia[23].

DVT in calf muscle veins

The distal DVT or calf veins occurs in infrapoplíteal veins, i.e., posterior tibial veins, peroneal veins and calf muscle veins (gastrocnemius and soleus plexus). While sensitivity and specificity of compression ultrasonography in proximal DVT are high and the treatment with anticoagulants is well established, distal DVT is less severe (50-75% sensitivity and 90-95% specificity). Unlike proximal DVT, the distal DVT diagnosis and treatment approach remain controversial[24-26].

Lagerstedt et al. (1985) showed that the use of anticoagulant for three months in patients with venous thrombosis in the calves significantly reduced recurrences and complications in symptomatic patients, compared to patients treated by other agents[27].

Philbrick et al., in a literature review of 20 studies, showed that calf thrombosis may spread proximally in about 20% of cases, and that anticoagulation in symptomatic patients may prevent the spread, embolization, and early recurrence. Follow-up for 1 week to assess the thrombus propagation is an alternative to anticoagulation[28]. A study by Lohr et al. showed that about 32% of patients presented signs of progression, and 75 patients (5%) presented signs suggestive of pulmonary embolism[29].

The CALTHRO study, conducted with 431 patients without proximal DVT, which evaluated the distal segment, showed that 15.3% of the sample had distal DVT. There was a significant difference in the onset of new events in three months among patients with distal DVT (5/64, 7.8% *versus* 3/351, 0.8%, p=0.003). The study then led the medical community to the conclusion that a negative outcome in patients with distal DVT who received no treatment may be relevant[30].

However, recent studies have shown that the importance of infrapopliteal DVT diagnosis and treatment can be at least questioned due to the absence of improvement as to recanalization, progression and complications, besides the fact that an increase in the number of diagnoses of distal DVT using vascular ultrasound may lead to an increase in the number of patients receiving oral anticoagulant therapy, thus resulting in excess treatment[25].

Clifford et al. performed a retrospective study and found no significant difference as to disease progression with anticoagulant treatment in patients with distal DVT[31].

In a randomized trial with 107 patients, 54 using low-molecular-weight heparin for a short period and 53 patients with venous compression, Schwarz et al. found no differences between groups as to pulmonary embolism, death occurrences, hemorrhage, and degree of recanalization[32]. Sule et al., on the other hand, showed no significant differences between the group receiving anticoagulation and patients who did not received it when it comes to the progression of disease, recanalization, pulmonary embolism and death occurrences[33].

Further randomized clinical trials evaluating the true effectiveness of anticoagulation in the treatment of distal DVT are thus needed. Righini et al. have been developing the CACTUS study, which was initiated in 2008 and is expected to be concluded in 2013. The authors expect to allocate about 600 patients in a randomized, double-blind study aimed to determine the effectiveness of nadroparin treatment (low-molecular-weight heparin) compared to placebo in patients with the first episode distal DVT.

The current recommendation of the American College of Chest Physicians[34] is to treat distal DVT with anticoagulants for three months. Given the conflicting results of studies presented here, the management of patients with distal DVT remains controversial in clinical practice. Recently, a systematic review by Masuda et al. analyzing over 1,500 articles on the subject, although there were no data that could clarify the controversy surrounding the best treatment for

infrapopliteal DVT, showed that due to the risk of propagation, pulmonary embolism, and recurrence, not taking any approach facing distal DVT should be unacceptable. In the absence of strong evidence, both anticoagulation and follow-up with imaging methods and selective anticoagulation remain as the acceptable treatment methods[35]. De Martino et al., in a recent meta-analysis aimed to evaluate the effectiveness and safety of anticoagulation in patients with calf DVT, showed that episodes of pulmonary embolism and propagation of thrombosis were less frequent among patients who received anticoagulants[36].

Vascular ultrasound has revolutionized the diagnosis and management of DVT, enabling a non-invasive and high-accurate management of several anatomical and functional features determined by the thrombus formation and sequelae. The clinical practice over the last 30 years have enabled a better understanding of many controversial issues, such as those presented throughout this literature review. However, there are still gaps that may only be filled by further studies conducted with adequate methodology.

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