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Full Length Article

Diagnosis of deep-vein thrombosis

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ABSTRACT

The diagnostic approach to suspected symptomatic deep-vein thrombosis of the lower extremities is usually based on non-invasive methods, including the estimation of clinical probability, the measurement of D-dimer levels, and ultrasonography. The present review discusses the evidence available from the literature about the management of the first episode of suspected deep-vein-thrombosis.

1. Introduction

For descriptive, as well as diagnostic and prognostic purposes, the deep veins network of the lower limbs is classically divided into two regions: the proximal and the distal territory. Noteworthy, proximal DVT is more frequently associated with pulmonary embolism (PE) [1], and recurrence [2] than isolated distal DVT. The former includes the femoral (common, superficial, deep or profunda) veins and the popliteal vein; the latter comprises the paired anterior and posterior tibial veins, and the peroneal veins, cumulatively known as axial, plus the muscular (gastrocnemius, soleal) veins [3]. The calf "trifurcation", formed by the joining of the tibial and peroneal veins, though formally belonging to the distal venous district, is usually screened when proximal CUS is performed. Finally, it is now commonplace to include in the proximal territory also the last 3 cm of the superficial veins close to the saphenous junctions.

In symptomatic patients, as shown by classic venographic studies, DVT invariably develops in the venous-valves sinuses of the distal network, extending to the proximal system, in the absence of prophylaxis or treatment, in 5–20% of the patients [4,5]. Conversely, in asymptomatic patients, DVT may arise anywhere in the deep-vein system [3]. This observation, along with the more common finding of small and non-occlusive thrombi, may account for the lower sensitivity of ultrasonography for asymptomatic DVT [6].

In recent studies, the prevalence of DVT in symptomatic patients was around 10–15%, suggesting a low referral-threshold, as compared with older (venographic) studies reporting figures as high as 35% [7]. Therefore, the main challenge for any diagnostic approach is to rule-out DVT safely (i.e., low incidence of thromboembolic events at follow-up in patients left untreated on the basis of normal findings, otherwise "cleared" from DVT) and efficiently (i.e., the proportion of patients in whom a given strategy may be safely applied). The commonly accepted safety threshold is below 2%, corresponding to the follow-up prevalence of DVT in patients with a normal venography [8].

Venography, the official "gold standard" for the diagnosis of DVT, is seldom used in everyday practice, being invasive, costly, technically demanding, painful, contraindicated in case of allergy or renal insufficiency, and difficult to interpret, with considerable inter- and intra-observer variability [5]. Alternative (invasive) imaging approaches, i.e.: CT- and MR-venography, not only share many of the same limitations of venography, but also do not possess adequate accuracy to be used as gold standard [5].

Current non-invasive diagnostic algorithms to rule-out suspected symptomatic DVT include pretest probability estimation, D-dimer, and ultrasonography [5,9,10]. We will discuss the relevant literature concerning those different strategies in the following sections. Noteworthy, only ultrasonography may be used a stand-alone test to rule-in or rule-out DVT.

1.1. Pretest probability

Although useful to raise the clinical suspicion of DVT, individual clinical features; such as, calf pain or swelling, warmth, tenderness, erythema, oedema, difference in calf diameter, Homan's sign, history of

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Table 1
The modified Wells DVT rule [12].

Clinical variable	Score[a]
Active cancer (treatment on-going or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)[b]	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	− 2

DVT: deep-vein thrombosis.

[a] Pretest probability scores may be categorized as follows: "high": ≥ 3; "moderate": 1–2; "low": ≤ 0. The post-test probability of DVT was reported to be: 53% in the high probability group, 17% in the intermediate probability group, and 5% in the low probability group, respectively [12]. Alternatively, pretest probability scores may be categorized as: "likely": ≥ 2, or "unlikely" ≤ 1; and the post-test probability of DVT was reported to be: 27% in the likely probability group, and 4% in the unlikely probability group [41], respectively.

[b] In patients with symptoms in both legs, the more symptomatic leg was used.

DVT, immobilization, recent surgery, malignancy, or obesity, are useful but not sufficient to rule in/out DVT [6].

Structured forms clinical judgment (decision rules), based on the cited individual clinical features, are instead valuable in that they allow patients to be assigned a definite pretest probability level, being the probability of DVT progressively higher in patients with higher scores [6,9,11]. According to international guidelines, the assessment of pretest probability should come first in the diagnostic pathway of suspected proximal DVT in symptomatic outpatients [5,10].

The more thoroughly studied and validated clinical decision rule, either in its dichotomized (likely, or unlikely) or tripartite (low, intermediate, high) set-up, is the Well's DVT rule (Table 1) [7,12,13]. According to a meta-analysis of 21 studies, assuming a 15% DVT prevalence, the Wells' rule would categorize 18% of the patients as "high risk" (Score: ≥ 3, DVT probability = 47%), 40% as "intermediate risk" (Score: 1–2, DVT probability = 12%), and 42% as "low risk" (Score ≤ 0, DVT probability = 4%) [6]. Given these post-test probabilities, the Wells rule cannot be employed as a stand-alone test to confirm or exclude DVT; thus, it is commonly associated with D-dimer or ultrasonography [5,9,10]. If neither D-dimer nor ultrasonography is readily available the Wells rule may be used to stratify patients, allowing for delayed testing in low- and moderate-risk patients, who may be safely and quickly discharged [14].

The value of the Wells DVT rule in both the primary care and the inpatient setting, as well as in patients with suspected isolated distal DVT, is disputed [6,13,15–18]. Particularly, in a study of primary care patients with suspected DVT, the safety of the Wells rule was challenged, being the probability of DVT as high as 12% in the low-risk group, as compared with 3% in the original Wells study; furthermore, despite the combination of a low score with a normal D-dimer, the observed DVT incidence crossed the standard 2% safety margin (2.3%, 95% CI, 1.9 to 2.7) [16]. Consequently, a group of 110 Dutch primary care practices proposed a different rule (the primary care, or Oudega rule, Table 2), combining clinical items with point-of-care qualitative D-dimer testing, for the exclusion of DVT in that setting [19]. In the original derivation study, the rule categorized 21% of the patients as "high risk" (Score: 10–13, DVT probability = 51.3%), 51% as "moderate risk" (Score: 7–9, DVT probability = 21.7%), 5% as "low risk" (Score 5–6, DVT probability = 4.5%), and 23% as "very low risk" (Score 0–3, DVT probability = 0.7%) [19]. These findings were

Table 2
The primary care rule [19].

Diagnostic variables	Points for the rule[a]
Male gender	1
Oral contraceptive use	1
Presence of malignancy	1
Recent surgery	1
Absence of leg trauma	1
Vein distension	1
Calf difference ≥ 3 cm	2
D-dimer abnormal	6

[a] High risk: 10–13; moderate risk: 7–9; low risk: 5–6; very low risk: 0–3. The post-test probability of DVT was reported to be: 51% in the high probability group, 22% in the moderate probability group, 4% in the low probability group, and < 1% in the very-low probability group, respectively [19].

subsequently externally validated in independent cohorts (Table 3) [20,21]. Furthermore, a recent head-to-head comparison study and a meta-analysis found that both rules are similarly safe in that setting (Table 3), the discrepancy being accounted for by the inclusion of a new item (history of DVT) in the Wells rule [9,22]. Accordingly, primary care guidelines for the management of patients with suspected DVT endorse the use of the Wells rule [10].

In hospitalized patients, the Wells rule performs poorly, since the probability of DVT in low-risk patients is disappointingly high, ranging between 6% and 12% (Table 3) [15,18]. Similarly, in patients with isolated distal DVT the rule displays unsatisfactory sensitivity, as the probability of DVT in low-risk patients ranges between 8% and 14% [13,15,17]. In addition, a recent meta-analysis challenged the usefulness of the Wells DVT rule in outpatients with malignancy, being the failure rate almost 2-fold as compared with non-cancer patients, and the efficiency lower than 10% [9]. Since D-dimer testing also possesses limited accuracy in inpatients, in patients with isolated distal DVT, as well as in those with cancer, it is feasible that such patients would be better off managed on the basis of ultrasonography alone [6,17].

Finally, experienced physicians or nurses may formulate quite accurate estimates of pretest probability, employing implicit or "gestalt" clinical judgment [13]; however, the gestalt approach obviously lacks reproducibility [6].

In conclusion, the Wells DVT rule is useful to stratify symptomatic outpatients for subsequent testing; namely: D-dimer if the probability level is either unlikely or non-high, or ultrasonography, if either a likely or high pretest probability is assigned. Hospitalized patients, as well as outpatients with malignancy, are probably better managed on the basis of ultrasonography.

1.2. D-dimers

D-dimers are specific cross-linked derivatives of fibrin, produced when fibrin is degraded by plasmin, so concentrations are raised in patients with venous thrombosis [23]. Numerous other conditions, such as older age, cancer, infection, inflammation, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm or aortic dissection, pregnancy, and recent trauma or surgery yield increased D-dimer levels, limiting the efficiency of D-dimer-based approaches [9,24,25]. In particular, it is noteworthy that normal D-dimer levels may be found in only 56% of healthy subjects with ≥ 70 years, as compared to > 90% of the general population under 50 years [26]. An age-dependent D-dimer cut-off (age × 10 mcg/L) has been evaluated in patients with suspected DVT and either an unlikely, or a non-high Wells score, [27,28]. The age-dependent cut-off is used in patients with > 50 years instead of the conventional 500 mcg/L cut-off, doubling the number of patients with ≥ 80 years in whom DVT can be excluded, with acceptable safety (Table 3) [27,28]. A large, prospective, multicentre study (ADJUST-DVT) testing the safety of withholding treatment