Chapter 20

DEEP VEIN THROMBOSIS

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Deep vein thrombosis (DVT) is characterized by the abnormal formation of blood clots in deep veins, resulting in constriction, obstruction, and collateral venous return. These clots can cause swelling, pain, ulceration, necrosis, disability, and, in severe cases, pulmonary embolism (PE), which can be fatal. The

incidence of DVT increases the risk of PE, making venous thromboembolism (VTE) a common cause of hospital death, affecting around 10 million people globally. Women between 20 and 40 years are at higher risk due to reproductive factors, while men are at higher risk in other age groups (Khan et al., 2021; Jiang et al., 2024).

In the United States, it is estimated that DVT affects up to 600,000 individuals annually, resulting in 100,000 to 180,000 deaths from VTE. DVT is considered a medical emergency requiring immediate attention (Brill, 2021). Upper extremity deep vein thrombosis (UEDVT) accounts for about 6% of DVT cases, being less common than lower extremity deep vein thrombosis (LEDVT) (Khan; Marmaro; Cohen, 2021).

Three main factors contribute to DVT formation: static blood flow, venous wall damage, and hypercoagulability. Recent studies have shown that neutrophil extracellular traps (NETs) are closely related to DVT (Yao et al., 2023). In diagnosis, color Doppler ultrasound has become essential due to its high sensitivity and accuracy. Diagnostic tests include sequential clinical evaluations and the D-dimer test, which, despite its moderate sensitivity, is complementary in diagnosis (Jiang et al., 2024).

For patients with intermediate to high-risk PE and signs of hemodynamic decompensation, thrombolytic therapy should be considered. DVT treatment is based on immediate anticoagulation, whose failure can worsen the disease (Yao et al., 2023). Pharmacological studies have shown that heparin, besides its preventive effect against DVT, reduces the expression of ITAM1, ITGAM, and fibronectin in thrombus tissue, which are critical in mediating platelet adhesion and binding (Li et al., 2020). The optimization of screening to assess the risk of venous thromboembolism (OPTIMEV) has provided relevant data for the treatment of isolated distal DVT of the lower limbs (Galanaud et al., 2023).

In diagnosis, several biomarkers, such as microRNA, interleukin-1, interleukin-8, and other inflammatory markers, have been investigated as predictive tools for DVT. However, no identified substance is sufficiently sensitive or specific to predict DVT diagnosis. Metabolomics, which studies the types and amounts of endogenous metabolites and their changes in response to external disturbances, is a promising approach to better understand the pathophysiology of DVT, identify biomarkers, and help develop accurate clinical diagnosis (Jiang et al., 2024).

As recurrent DVT is a significant risk factor for post-thrombotic syndrome (PTS), proper anticoagulation management remains a challenge. Although no specific anti-inflammatory effect has been reported for DOACs, these drugs target two coagulation factors with pro-inflammatory properties. Recent studies show that dabigatran may have anti-inflammatory effects, while the use of direct oral FXa inhibitors, such as rivaroxaban, significantly reduces PTS. Patients treated with rivaroxaban for six months had better outcomes compared to those treated with conventional therapy overlapped with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) (Borgel et al., 2019).

EPIDEMIOLOGY

VTE, which includes DVT and PE, is a frequently underestimated vascular condition. In Western regions, approximately 1 in 12 individuals will be diagnosed with VTE during their lifetime, with an incidence rate of about 1-2 per 1,000 person-years in Europe and the USA. In contrast, rates are lower in Asia, such as in South Korea, where the incidence is 0.2 per 1,000 person-years. In the USA, it is estimated that there are approximately 1,220,000 annual cases of VTE, with about 370,000 cases of PE and 857,000 cases of DVT (Lutsey and Zakai, 2023).

Risk factors for VTE include obesity, lack of physical exercise, adverse social conditions, and missed prevention opportunities during hospitalization. In patients with incurable cancer, VTE is treated with anticoagulants indefinitely, while hormone-associated VTE in women receives limited treatment. Surgery and bone fractures are established risk factors for VTE. The postoperative risk varies with the type of surgery and is influenced by factors such as advanced age, male sex, obesity, active cancer, malnutrition, pneumonia, blood transfusions, and myocardial infarction (Lutsey and Zakai, 2023). Long bone fractures of the leg, trauma-related fractures, and surgically treated fractures pose a higher risk for VTE.

Between 40% and 60% of all VTE events occur during or within three months after hospitalization, increasing the risk by approximately 100 times. Hospitalization for infection in the past 30 days increases the risk of VTE by 2.7 times, while antibiotic treatment increases the risk fivefold during use (Lutsey and Zakai, 2023). DVT is a significant medical condition that frequently occurs in traumatic orthopedics, mainly associated with periprosthetic and lower limb fractures. These fractures account for over 95% of DVT cases in traumatic orthopedics, while DVT in upper limb fractures is rare, with a global incidence of only 0.69%. DVT can lead to prolonged hospitalization and increased hospital expenses, as well as severe complications such as post-thrombotic syndrome (PTS) and PE, which can severely affect the patient's quality of life and even result in death (Hu et al., 2023).

Perioperative DVT can be classified as preoperative and postoperative, depending on the time of occurrence. Preoperative DVT is particularly concerning as it can delay surgery, affecting optimal timing and surgical outcomes. If a thrombus is not detected in time preoperatively, orthopedic surgery can cause thrombus rupture, leading to PTS, PE, and other adverse outcomes. Despite these distinctions, existing guidelines do not differentiate preoperative from postoperative DVT in terms of screening and diagnostic strategies (Hu et al, 2023).

Studies on the prevalence of preoperative DVT in patients with long bone fractures of the lower extremities suggest considerable variability. In patients with proximal femur fractures, the reported prevalence was 52.50%, while studies in Hong Kong showed a prevalence of only 5.3% without thromboprophylaxis in elderly Chinese patients with

hip fractures. One study revealed a preoperative prevalence of 43.92% in tibial plateau fractures, while another reported only 16.3% (Hu et al., 2023). These discrepancies indicate the need for standardization in screening and diagnostic practices.

Adham et al. (2021) investigated the prevalence of occult cancer in patients with unprovoked VTE. The rate of diagnosed occult cancer using the CT-based strategy was 12.8%. Yamashita (2021) revealed a prevalence of approximately 5% of upper extremity DVT among patients with DVT. In a prospective cohort, 33% of patients with upper extremity DVT had a central venous catheter or pacemaker, and 29% had active cancer. During anticoagulant therapy with DOACs, the annual incidence rates of recurrent VTE and major bleeding were 0.9% and 1.7%, respectively. After discontinuation of anticoagulant therapy with DOACs, the annual incidence rate of recurrent VTE was 3%.

DIAGNOSIS

Early diagnosis of DVT is crucial as incorrect diagnoses can lead to significant consequences. Patients incorrectly identified as having DVT (false positives) are treated with anticoagulation, exposing them to unnecessary costs, inconveniences, and bleeding risks. Conversely, patients incorrectly diagnosed as not having DVT (false negatives) risk extension and embolization of DVT in the absence of treatment (Bhatt et al., 2020).

DVT is often unilateral and should be clinically considered in patients presenting with acute pain, swelling, tenderness, edema, erythema, and/or warmth in the affected lower extremity, with the popliteal vein being a common site for DVT (Bhatt et al., 2020; Nakayama et al., 2023). Approximately 80% of PE cases result from DVT in the lower extremities (Hamamoto et al., 2022). These manifestations, however, are nonspecific, and besides preclinical risk assessment, objective tests are necessary. Early diagnosis and clinical intervention are essential for managing DVT, minimizing adverse consequences, and avoiding additional costs and risks of anticoagulant therapy for patients without the disease (Bhatt et al., 2020).

Rapid identification and efficient treatment are crucial for reducing health risks and improving clinical outcomes. Currently, various clinical, laboratory, and imaging tools are available for diagnosis. Traditional DVT diagnosis often involves CUS of the proximal leg vein. However, about 20% of DVT cases show negative results with this method, leading to the development of strategies for better screening of suspected patients. When a CUS is necessary but results negative and the D-dimer is positive, the CUS should be repeated 6 to 8 days later to assess for a possible undetected distal DVT.

The Second Consensus on Diagnosis and Treatment of DVT issued by the European Society of Cardiology (2022) and the 9th American College of Chest Physicians (2022) recommend clinical risk stratification of DVT using the Wells Score. Pre-test probability assessments, such as the Wells score, and the D-dimer test have been adopted to optimize

the diagnostic pathway, although the process can be complex and time-consuming (Appel et al., 2020). This score evaluates signs, symptoms, and VTE risk factors to categorize the probability of lower extremity DVT as low, intermediate, or high. In patients with low or intermediate risk of DVT, D-dimer level measurement is recommended. If the D-dimer is positive, whole-leg ultrasonography (US) is suggested. However, in patients with a high risk of DVT, it is recommended to perform US without measuring D-dimer levels (Hamamoto et al, 2022).

Objective diagnostic tests with high sensitivity and specificity are essential to exclude or confirm the diagnosis of DVT. Diagnostic modalities include D-dimer assays and CUS. D-dimer, a fibrin degradation product, is usually elevated in the presence of DVT. Although highly sensitive, D-dimer is often elevated in the presence of inflammation, malignancy, and other systemic diseases, being nonspecific and requiring additional tests if elevated (positive) or if the clinical probability of DVT is not low. CUS evaluates the compressibility, or lack thereof, of a venous segment to diagnose thrombosis, often associated with color Doppler to assess blood flow. In acute DVT, compressibility is lost due to passive vein distension by a thrombus. CUS can be limited to the proximal leg veins or performed on the entire leg (whole-leg CUS). US can also be performed sequentially, known as serial US (Bhatt et al., 2020).

Highly sensitive ELISA or immunoturbidimetric D-dimer tests should be measured in patients with "unlikely" clinical probability to exclude DVT diagnosis. Venous ultrasonography is recommended as the first-line imaging method for DVT diagnosis and can also be proposed in the case of confirmed PE for initial venous imaging, useful in case of suspected recurrent DVT or additional stratification in selected patients. Venous magnetic resonance imaging should be reserved for selected patients, such as in the scenario of recurrent ipsilateral DVT, a challenging diagnosis since persistent intravascular abnormalities after previous DVT often hinder compression ultrasonography diagnosis. Similarly, these residual vascular abnormalities complicate the interpretation of all other diagnostic modalities, including contrast venography.

Magnetic resonance direct thrombus imaging (MRDTI) is a technique with a short acquisition time (10 minutes) that relies on methemoglobin formation in a fresh thrombus, appearing as a high signal when viewed in a T1-weighted MRI by measuring the T1 shortening signal. This technique does not require intravenous gadolinium contrast. MRDTI can accurately diagnose a first DVT and distinguish acute recurrent DVT from chronic residual thrombotic abnormalities with sensitivity and specificity of at least 95%. MRDTI, therefore, has the potential to be used as a single test to diagnose or rule out recurrence (van Dam et al., 2020).

RECENT ADVANCES IN DVT DIAGNOSIS

Recently, the Regional Hospital of Silkeborg in Denmark implemented a new protocol for direct access to whole-leg compression ultrasonography for patients with suspected DVT referred by family doctors. It was found that a single whole-leg CUS captures distal DVT, eliminating the need for repeated CUS. This method allowed for same-day investigations, eliminating the need for additional tests such as D-dimer and significantly reducing the time and resources required for early diagnosis. The differentiated approach resulted in a remarkable decrease in resource usage compared to traditional diagnostic methods, highlighting its feasibility and effectiveness in clinical practice. The pathway did not include patients with pulmonary symptoms, which raise the suspicion of pulmonary embolism. In Denmark, these patients are referred directly to critical care procedures. Sixty percent of all patients were seen with an average time of 24 minutes without the need for hospitalization. The direct same-day pathway provided approximately 60% reduction in resource usage (Appel et al., 2020).

Whole-leg CUS and proximal leg CUS are clinically equivalent methods for diagnosing DVT. Whole-leg CUS has the advantage of not requiring repetitions to detect if an isolated distal venous thrombosis has progressed to proximal veins, reducing hospital visits. However, its frequent use may increase the detection of distal thromboses, raising concerns about overtreatment, given that isolated distal deep vein thrombosis (IDDVT) is generally considered less severe. Studies highlight the importance of surveillance to prevent late complications such as post-thrombotic syndrome. Additionally, whole-leg CUS can identify other pathologies, improving overall diagnostic efficiency. Thus, while effective, its use should be balanced with considerations of potential clinical impacts and costs associated with the treatment of detected IDDVT (Appel et al., 2020).

An Italian study used the Nominal Group Technique (NGT) to reach consensus among experts on the management of DVT and pulmonary embolism in the emergency department. Despite advances, many low-risk patients are unnecessarily admitted, suggesting the need for clear guidelines for outpatient management. Experts reviewed recent evidence and developed consensus statements that address from initial suspicion to acute treatment of these conditions. Recommendations such as the use of the Wells score for risk stratification, D-dimer testing, and the preference for DOACs were highlighted as fundamental for evidence-based clinical practice. The application of NGT proved effective in integrating clinical and scientific perspectives, promoting standardization and continuous improvement in the quality of emergency healthcare. This structured approach not only facilitates early and accurate diagnosis but also optimizes patient management, resulting in better clinical outcomes and efficiency in care (Salvi et al., 2020).

Due to high morbidity and mortality in hospitalized patients and diagnostic criteria failures, a study was conducted at Kagoshima University between January 2017 and

December 2018 on patients undergoing planned surgery under general anesthesia. The aim was to develop a new pre-test probability score for DVT diagnosis in patients before surgery under general anesthesia, considering: D-dimer greater than or equal to 1.5 (2 points), age over 60 years (1 point), positive family history of DVT (1 point), glucocorticoid use (1 point), high-risk cancer for DVT (1 point), and prolonged immobilization (1 point). The Kagoshima-DVT score divided patients into low, medium, and high-risk groups, considering scores from 0 to 7. The initial probability score proved effective in diagnosing DVT in hospitalized and outpatient patients before surgery. It was possible to distinguish a low-probability group that did not require full-leg ultrasonography and a high-probability group that had more DVT cases identified before surgery (Hamamoto et al., 2022).

Another recent study, named Theia, was a diagnostic management study conducted in 5 university hospitals and 7 non-academic hospitals in 5 countries. Between March 2015 and March 2019, patients aged 18 years or older presenting with clinical suspicion of acute recurrent ipsilateral leg DVT were included. The aim of the research was to evaluate the use of direct thrombus magnetic resonance imaging (ITMR), a technique without the need for intravenous contrast and with a 10-minute acquisition time, capable of accurately differentiating acute recurrent DVT from chronic residual thrombi. The safety of ITMR as the only test to rule out recurrent ipsilateral DVT was evaluated. Patient treatment was determined based on the ITMR result, performed within 24 hours after inclusion in the study. The study concluded that the rate of new VTE episodes after a negative ITMR result was low. This exam proved to be a simple, practical, and reliable diagnostic tool (van Dam et al., 2020).

TREATMENT

Acute DVT can be treated on an outpatient basis with anticoagulant therapy, reserving hospitalization for patients with severe symptoms. Initially, hospital treatment involves intravenous heparin use, followed by a transition to oral or subcutaneous anticoagulant therapy for three months. In more complex cases, invasive treatment options are indicated, such as catheter-directed thrombolysis (CDT), pharmacomechanical CDT, and percutaneous mechanical thrombectomy (PMT) (Sailer et al., 2022).

CDT and pharmacomechanical CDT require ICU admission, representing a significant economic burden on the healthcare system. In contrast, PMT does not use thrombolytic agents, reducing bleeding risk and eliminating the need for ICU admission. This technique allows the removal of all types of thrombi, including subacute and chronic clots. Indications for invasive treatments include emergencies such as threatened limb or clot progression in the inferior vena cava during anticoagulant therapy, anticoagulant therapy failure, prevention of post-thrombotic syndrome (PTS), or progression of PTS in patients with iliofemoral DVT or moderate to severe PTS (Sailer et al., 2022).

Phlegmasia cerulea dolens is a rare but potentially fatal complication of acute DVT, characterized by severe limb swelling, pain, and cyanosis, potentially leading to arterial ischemia and gangrene, with high amputation and mortality rates. Iliofemoral DVT differs from femoropopliteal DVT as it is associated with more frequent recurrences and more severe PTS due to the anatomical characteristics of the lower limb venous system. While femoropopliteal or distal DVT is more easily compensated by collateralization, iliofemoral occlusion has little chance of sufficient collateralization. However, some cases develop adequate collateralization, directing venous return to the ipsilateral and contralateral iliac system, quickly relieving symptoms (Kim; Choi and Kim, 2021).

For asymptomatic proximal DVT, anticoagulant treatment alone is sufficient to reduce recurrence rates and prevent PE. There is no need for endovascular thrombus removal in patients with isolated distal DVT, as the risk of PE is low. The need for anticoagulant treatment for isolated distal DVT has not yet been established, varying between centers and clinicians (Kim; Choi and Kim, 2021).

Minimally invasive techniques have been used in DVT treatment, such as autonomous percutaneous mechanical thrombectomy, which fragments and aspirates thrombi; catheter-directed pharmacomechanical thrombolysis (PCDT), combining CDT with PMT; stent placement, especially in cases of iliac vein or inferior vena cava (IVC) obstruction; and concomitant anticoagulant treatment with unfractionated heparin during and after endovascular procedures. These techniques have been effective in reducing acute symptoms and preventing complications such as post-thrombotic syndrome (Kim; Choi and Kim, 2021).

Direct oral anticoagulant therapy has also been a safe and efficient approach to preventing recurrences, although its effectiveness as monotherapy in severe DVT cases is limited. Studies indicate that these combined approaches not only accelerate recovery but also reduce treatment time and the need for hospitalization, providing a better quality of life for patients (Kim; Choi and Kim, 2021).

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