VENOUS THROMBOEMBOLIC DISEASE: FROM DIAGNOSIS TO TREATMENT

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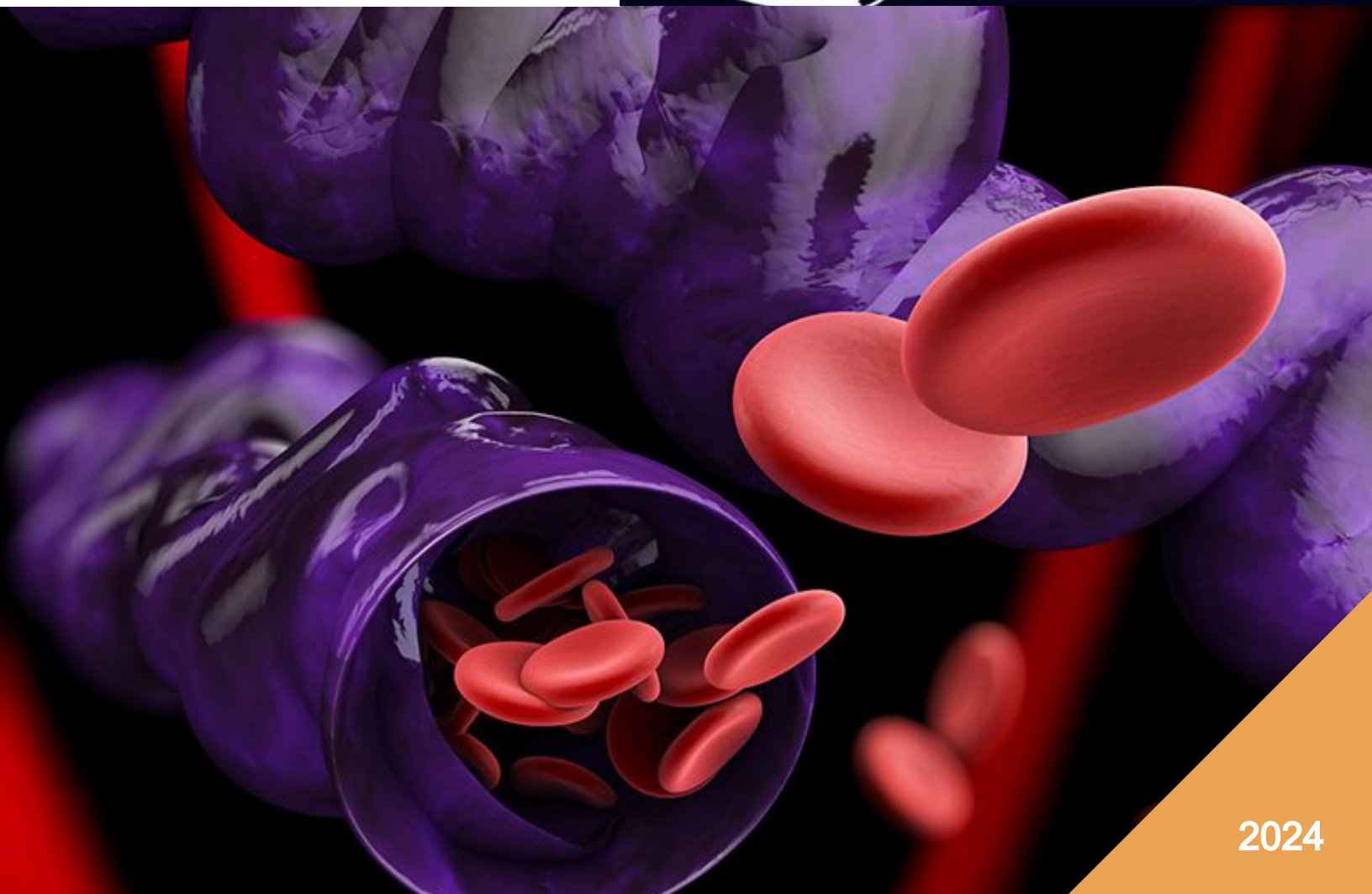

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DEDICATION

I dedicate this work to those who have been unconditionally by my side throughout every moment of my life: my family. Especially to my son, to whom I strive to pass on the legacy inherited from my parents: that knowledge and freedom are the greatest assets of an individual.

ACKNOWLEDGMENTS

My sincere gratitude to all the collaborators and colleagues at MECSMA (UniFOA) who accompanied and assisted me on this journey, and to everyone who supported this project. I would also like to thank all those who have been a part of my academic and professional development over the years.

PRESENTATION AND INSTRUCTIONS FOR USE

This e-book aims to assist in learning about venous thromboembolic disease, enabling final-year medical students to expand their knowledge on the subject in such a comprehensive way that it allows them to apply it in daily medical practice safely and accurately, always for the well-being of their patients.

It was developed under the light of meaningful learning theory, aiming to add updated knowledge about the disease to the reader's previously acquired knowledge during their training. As a digital book (e-book), it incorporates digital technology, aligning with the current reality of education. Additionally, it has an interactive nature intended to make the reading experience more dynamic, enjoyable, and complete.

Throughout the text, hyperlinks will be highlighted (in blue) and underlined. Clicking on them will open new "windows" with additional content in various forms: videos, animations, figures, concept maps, texts, and photos. In the bibliographic reference section of each chapter, the scientific articles used as the basis for the research and creation of the e-book will also be underlined and highlighted in blue, allowing access to them in PDF format.

The e-book can be accessed from any digital device (including smartphones or tablets) connected to the internet, through the website www.dtev.com.br. However, for a better experience, we recommend using larger screens, such as laptops or desktops.

Welcome to the e-book "VENOUS THROMBOEMBOLIC DISEASE: FROM DIAGNOSIS TO TREATMENT." We wish you an excellent reading experience and hope the content enhances your training.

PREFACE

When I received a message from Luis Fernando saying that he was in the final stages of his master's degree and that the final product of his postgraduate work would be an interactive ebook on venous thromboembolism, aimed at medical students in their professional cycle, covering all the relevant aspects—from epidemiology, risk factors, pathophysiology, diagnosis, treatment, to prophylaxis—I was filled with immense pride. The ebook would utilize well-established concepts of good medical practice along with the latest knowledge, with the goal of developing the student's clinical reasoning on a topic of high morbidity and mortality and significant social impact. To paraphrase the renowned German physician, pathologist, anthropologist, and politician, Rudolf Ludwig Karl Virchow: "Medical education does not exist merely to provide students with a means of making a living, but to ensure the health of the community."

Moreover, Luis Fernando was particularly persuasive, reminding me of his time as a medical resident, during which I had the pleasure of being his preceptor. The days of rounds, with case discussions and disease reviews, combined with the frequent on-calls triggered by emergencies, as well as the elective surgery days at the Central Hospital of the Military Police, where we all shared sun-dried tomato and arugula pizza, brought back a wonderful sense of nostalgia. It is truly a unique memory, as Luis is one of my most esteemed, brilliant, and beloved disciples.

To top it off—Luis Fernando told me that he would like the preface of the book to be written by the person who was most influential in his training. I don't need to say that my eyes filled with tears, and without hesitation, I immediately accepted the surprising invitation to write it.

It took me over a week to complete this task of great honor, as the responsibility weighed heavily on me, compounded by my busy schedule divided among UERJ, PMERJ, SBACV, and my private practice. I was unsure where to begin or how to address the range of issues that Luis, with incredible subtlety, managed to simplify and express so well in words. And I had even less idea how to conclude with a preface worthy of the said ebook.

After finishing reading the beautiful work, I can confidently recommend it. The language is clear, making the book an easy, quick, and practical reference, capable of addressing the doubts of young students and becoming a go-to resource for resolving day-to-day situations.

To experience the honor of writing a preface for a text created by a former student who has become a great colleague in our specialty is a unique emotion. As the father of modern pathology and social medicine, and the creator of the important Virchow's triad in VTE, once said: "Only those who consider healing as the ultimate goal of their efforts can be designated as physicians."

Happy reading to all!

Francisco João Sahagoff de Deus Vieira Gomes

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SUMMARY

INTRODUCTION

Introduction

The formation of thrombi is a process intended to protect the human body against injuries that damage vascular structures, potentially causing excessive and even fatal bleeding. However, when this process occurs without this specific protective purpose, affecting a closed vascular system, the thrombus will occupy the lumen of the blood vessel, obstructing blood flow through the local accumulation of cells and blood elements, leading to various consequences.

Thrombosis, therefore, is a phenomenon that occurs due to the formation of these thrombi ("clots") within blood vessels, which can affect both arteries and veins. The process of thrombus formation causes local inflammatory reactions that also affect the vessel wall, leading to structural changes that, in turn, can cause complications and sequelae of varying severity.

In arteries, thrombosis is generally associated with atherosclerosis and chronic inflammatory reactions that lead to the formation of plaques. When these plaques become unstable, they can fragment and stimulate the formation of thrombi at the site. These arterial thrombi lead to varying degrees of vessel obstruction and, consequently, ischemia of the tissue supplied by the affected vessel, potentially leading to tissue necrosis. In the case of coronary artery involvement, these obstructions can result in acute myocardial infarction (AMI), and in the case of cerebral arteries, they can lead to ischemic stroke.

Deep vein thrombosis (DVT), as the name implies, is characterized by the formation of thrombi within deep veins, which are located beneath the muscle fascia. The most common location for these thrombi is the lower limbs, but they can also occur in the upper limbs or central veins, located in the pelvis, abdomen, chest, or neck. When affected by a thrombotic process, these veins can be partially or completely obstructed.

Pulmonary thromboembolism (PTE), or pulmonary embolism, is considered the most feared complication of venous thrombosis. It occurs when a thrombus detaches from its original site and travels through the venous circulation, reaching the right chambers of the heart and, eventually, the pulmonary circulation. In the pulmonary circulation, the detached thrombus, now called an embolus, obstructs one or more arteries, leading to tissue death through an ischemic process.

The term superficial thrombophlebitis is used to describe the formation of thrombi in the so-called superficial veins, which are located above the muscle fascia. Theoretically, superficial thrombophlebitis has a significantly lower potential for embolization compared to deep thrombosis, but it can still lead to this type of complication.

Given that this condition has a wide spectrum of presentations, with various manifestations and complications, the term venous thromboembolic disease (VTE) encompasses both venous thromboses and pulmonary embolism.

To grasp the true significance of the impact of VTE and its complications, it is essential to note that pulmonary embolism is the leading cause of preventable deaths in hospitals and the third leading cause of cardiovascular deaths worldwide, surpassed only by AMI and ischemic stroke.

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PATHOPHYSIOLOGY AND RISK FACTORS

PATHOPHYSIOLOGY AND RISK FACTORS

Hemostasis is the physiological mechanism used by the human body to maintain circulatory integrity, especially after vascular injury. When a trauma occurs in the vessel wall, resulting in blood loss, a series of immediate physiological events are triggered to repair the injury, both by the parietal cells and blood elements, in an attempt to stop the leakage—primarily through the recruitment of platelets, which play a key role in thrombus formation.

Under normal conditions, the human body maintains a delicate balance between multiple endogenous procoagulant and anticoagulant components, ensuring blood homeostasis. A healthy and intact endothelium continuously expresses factors like thrombomodulin, tissue factor, endothelial protein C receptor, coagulation inhibitors, and heparin-like proteoglycans that produce an anticoagulant effect, inhibiting thrombus formation. When there is a reduction in these intrinsic anticoagulant factors or an increase in coagulation factors, there is a significant rise in the risk of thrombosis development.

In addition to the imbalance of these factors that can lead to hypercoagulability, there are two other factors that increase the likelihood of thrombus formation: endothelial injury to the inner vessel layer and blood stasis. These three factors (hypercoagulability, endothelial injury, and blood stasis) form Virchow's triad, described by the German physician Rudolf Ludwig Karl Virchow in the 19th century, which alone or in combination increase the risk of developing VTE.

The formation of a thrombus in the deep venous system most commonly occurs in the veins of the lower limbs, in areas of low flow such as the valve cusps or venous bifurcations. Once a thrombus is formed, there is a high chance of its propagation and growth due to the accumulation of cells and blood elements, further enhancing hypercoagulability through local hypoxia and hemoconcentration, which promote thrombus enlargement and propagation.

These thrombi generally form in smaller veins, most commonly in the calf's muscular veins, and can extend to larger veins (in about one-third of cases), significantly increasing the risk of pulmonary embolism.

Embolism occurs when the thrombus or a fragment of it detaches and travels through the venous system toward the right chambers of the heart. From the heart, it is ejected into the pulmonary circulation, where it causes arterial obstruction. The severity of the condition depends on various factors, but primarily on the degree of arterial obstruction, which causes ischemia in the pulmonary tissue and a consequent reduction in gas exchange areas.

VTE can be classified, for understanding its triggering factors, into provoked and unprovoked. The term unprovoked VTE refers to thromboembolic events not associated with external or environmental factors such as gender, advanced age, or intrinsic conditions known as hereditary thrombophilias. On the other hand, provoked VTE refers to risk factors caused by environmental or acquired factors, which can be either transient (such as pregnancy, estrogen use, trauma) or permanent (such as heart failure, venous insufficiency, obesity).

The risk factors associated with VTE development can also be classified according to their probability of causing the disease into strong, moderate, or weak. Notably, trauma and surgeries, particularly major oncological and orthopedic surgeries, are among the strongest risk factors for VTE development. The immobility caused by trauma and surgery, with consequent blood stasis and exacerbated inflammatory response, is significantly related to an increase in VTE cases in the absence of adequate prophylaxis.

Based on the likelihood that a particular risk factor is related to the disease, they are classified as strong when there is a high probability of being the causal factor, moderate when this relationship is probable, and weak when it can only partially explain the thromboembolic event.

Both genetic and environmental factors can contribute to the increased risk of VTE, making this disease often complex due to the interaction of various factors in a single patient. However, it is important to note that some cohort studies indicate that up to 50% of VTE cases may not have identifiable risk factors.

Venous stasis related to bed rest or long journeys is also associated with an increased risk of VTE development. Recent hospitalization is

noted in up to half of patients with VTE. Long-distance travel (>10,000 km) is a real but uncommon cause of VTE, affecting 4.8 per million passengers. One study estimated that the risk of symptomatic DVT two months after a long-haul flight would be one case per 4,500 flights.

Pregnancy and the postpartum period present a high-risk period for VTE development due to a state of hypercoagulability with changes in some coagulation factors that help prevent hemorrhagic events. Notably, there is an increase in factors VII, VIII, X, von Willebrand factor, and fibrinogen, with a decrease in protein C and the development of resistance to protein S, which are endogenous anticoagulants. These changes significantly increase the risk during pregnancy and the postpartum period, known as the puerperium, when half of the cases occur. The risk of developing the disease peaks in the first two weeks of the puerperium and extends up to the 12th week postpartum.

Advancing age alone can be considered a risk factor for VTE development, often exacerbated by the presence of additional factors such as various comorbidities acquired over the years. Some procoagulant factors, such as factors VII, VIII, fibrinogen, and homocysteine, have increased levels in the elderly, increasing their likelihood of developing the disease.

Hormonal therapy with estrogen and progestogens is associated with an increased risk of VTE in users due to the elevation of some coagulation factors, such as VIII, IX, X, and the reduction of endogenous fibrinolytic capacity, notably protein S.

Oncological diseases are related to the increased production of endogenous procoagulant substances, which can increase the risk of VTE by up to seven times in these patients. High-grade tumors and those in more advanced stages, with the presence of metastasis, are associated with a higher incidence of VTE, as are colon and pancreatic tumors.

Obesity is associated with an increased occurrence of venous thrombotic events due to the production of cytokines by adipose cells, creating a pro-inflammatory environment that, in turn, increases platelet adhesion and decreases fibrinolytic activity. These biochemical changes, combined with the mechanical alterations of obesity, such as increased intra-abdominal pressure hindering venous return and increasing stasis, are involved in the higher likelihood

of obese individuals developing VTE.

The association between VTE and smoking appears to be dose-dependent, with increased nicotine levels reducing nitric oxide production, creating a more inflammatory environment, increasing platelet adhesion, and consequently raising the likelihood of thrombus formation.

Some studies demonstrate an association between diabetes and increased incidence of VTE. Although this relationship is not fully elucidated, there is evidence of increased thrombin production in type 2 diabetic patients, raising the risk of thrombosis.

Some syndromes are associated with thrombosis caused by secondary factors, such as Mondor's syndrome, which is a thrombophlebitis of the breast veins usually associated with an oncological condition. Another is Lemierre's syndrome, which is a rare thrombosis of the internal jugular vein associated with oropharyngeal infection. Paget-Schroetter syndrome is thrombosis of the subclavian vein related to repetitive upper limb exertion that can affect young individuals engaged in intense physical activities.

In summary, both genetic and environmental factors can contribute to an increased risk of VTE, making this disease complex, often due to the interaction of various factors.

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EPIDEMIOLOGY

EPIDEMIOLOGY

The actual incidence of VTE (Venous Thromboembolism) is reported variably in the literature, and in Brazil specifically, there is a lack of precise data and more epidemiological studies on the subject.

According to 2020 data from the Centers for Disease Control and Prevention (CDC), it is estimated that each year, up to 900,000 Americans are affected by VTE, and between 60,000 to 100,000 die from pulmonary embolism during the same period. Furthermore, the CDC reports that among fatal cases, 25% manifest as sudden death, completely eliminating the possibility of treatment and altering the disease's prognosis.

The latest consensus from the European Society of Cardiology (ESC) in 2019 estimated the global incidence of pulmonary embolism to be 39 to 115 cases per 100,000 people. However, according to some studies, this real incidence is still underestimated because many cases, especially the milder ones, go undetected and undiagnosed.

Accurate data on the incidence of VTE in Brazil are still significantly scarce, with some of this data obtained through autopsies. A study on VTE mortality rates between 1989 and 2010, published recently, showed that among the 20,927,857 deaths in Brazil during this period, 92,999 had pulmonary embolism as the primary cause.

The number of deaths from pulmonary embolism in Brazil between 2016 and 2020 was 34,177, with the majority being women (58.1%). However, as age increased, the crude mortality rate also increased in both genders, with no statistically significant difference between men and women.

Data from DATASUS shows that between 2015 and 2019, the costs of treating pulmonary embolism in Brazil exceeded 76 million Reais.

Global estimates of the number of deaths caused by VTE are methodologically difficult to determine, as most data in the literature correspond to the reality of each country.

Despite the mortality associated with VTE decreasing over the past three decades in North America, in some countries, study data suggests that these numbers remain stable.

The improvement in diagnostic techniques and the evolution of therapeutic methods have generally led to a decrease in the incidence and mortality related to VTE from 12.8 to 6.5 per 100,000 people/year, with no substantial differences by sex.

In certain specific populations, such as pregnant women, oral contraceptive users, cancer patients, and the elderly, the higher incidence of VTE is well established.

Although the relationship between VTE and gender is not entirely clear, the incidence appears to be higher among men than among women in some studies. In terms of location, the incidence of proximal DVT is higher in men, while distal DVT is higher in women.

Regarding age, the higher morbidity of VTE in patients over 60 years old is related to the increased predisposition to thrombus formation due to degenerative endothelial changes brought about by aging.

Another factor related to aging is the higher predisposition to various diseases that can increase the incidence of VTE, such as cancer.

Concerning race/ethnicity, in Brazil, a higher mortality rate from VTE has been observed among whites, but these numbers may be more related to other factors such as lifestyle, genetic, environmental, social factors, and dietary habits rather than ethnicity itself. In the United States, the mortality rate is higher among African Americans, further corroborating the influence of various factors that vary according to the studied location.

VTE is a common complication in hospitalized patients and, despite its high incidence, often presents with nonspecific or even mild symptoms, making detection difficult. As a disease that can have a silent and potentially fatal course, affecting up to 60% of hospitalized patients and responsible for 5% to 10% of deaths, it is crucial to be vigilant for the slightest signs and dedicated to preventive measures.

Cancer patients, for example, have a fourfold increased risk of developing venous thromboembolic events due to the presence of cancer cells that produce procoagulant substances, while cytotoxic agents used in treatment can increase the chance of these events by 2.2 times.

Pregnant women may have a sixfold increased risk of developing VTE, most notably in the third trimester of pregnancy and especially during the postpartum period, within the first six weeks after childbirth.

The use of oral contraceptives containing both estrogen and progestogens is directly involved in increasing the risk of VTE by up to three times, and this number can be even higher in patients with an associated thrombophilia.

Advancing age is a well-known risk factor for VTE. In elderly individuals over 80 years old, the risk of the disease can be up to 80 times higher than in the population aged 25 to 30 years.

The incidence of VTE in long-term smokers (one pack/day for more than 20 years) has been shown to be higher than among non-smokers, potentially being 1.5 times greater compared to non-smokers.

The figures related to VTE can indeed vary, and more studies on the subject are truly needed to better understand the disease's behavior in different localities according to the data from each country.

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DIAGNOSIS

DIAGNOSIS

The importance of a rapid and accurate diagnosis of VTE, including deep vein thrombosis, complicated embolism, and uncomplicated embolism, is directly related to the early initiation of treatment. This helps prevent the progression of the disease and its severe complications, which significantly increase mortality rates.

Approximately 2/3 of patients diagnosed with VTE present with deep vein thrombosis (DVT), and up to 1/3 may present with pulmonary embolism (PE). Therefore, an accurate diagnosis is essential for initiating the correct treatment, as it has a profound positive impact on the disease's progression. On the other hand, an erroneous diagnosis of VTE leading to the use of anticoagulants without proper indication poses considerable risks to the patient, primarily due to potential complications such as bleeding.

Suspicion of VTE arises when a patient presents with clinical signs suggestive of the disease, especially when associated with one or more risk factors. However, confirmation through complementary diagnostic methods is always necessary.

The clinical signs and symptoms of VTE can be quite variable, atypical, or even absent. In the case of deep vein thrombosis in the limbs, the patient may experience pain, increased tenderness, edema, a sensation of heaviness, cramps, dilated superficial veins, and a reddish or purplish discoloration of the limb.

During physical examination, certain signs may raise suspicion of the disease, such as pain triggered by dorsiflexion of the foot (Homans' sign), pain upon compression of the muscle against the bone (Bancroft's sign), and reduced mobility upon calf compression (Flag sign).

Patients with pulmonary embolism more commonly present with cardiorespiratory symptoms, with chest pain and tachypnea being the most frequent, possibly associated with or without tachycardia. Physical examination may reveal crackles, diminished breath sounds, signs of pulmonary hypertension such as jugular vein distension, and an accentuated second heart sound (B2). In more severe cases, the patient may present in cardiogenic shock.

There is no pathognomonic presentation for VTE, and the signs and symptoms of both DVT and PE are variable, depending on factors such as thrombus size, embolic load, presence of comorbidities, age, among others. It is important to note that up to 70% of patients with PE may have asymptomatic DVT, and less than half of confirmed DVT cases exhibit characteristic symptoms.

Given that the likelihood of accurately diagnosing VTE based solely on history and physical examination is low, Wells, in 1997, established a clinical prediction model based on symptoms, signs, differential diagnoses, and risk factors to predict the probability of VTE. This model is known as the Wells criteria (or Wells score).

Another score used to assess the probability of VTE diagnosis is the Geneva score, which, according to studies, has lower predictive power compared to the Wells score. with the latter being more widely used and disseminated around the world as a model to increase the chances of a correct diagnosis.

The measurement of serum D-dimer levels can assist in the diagnosis of VTE. As a fibrin degradation product, D-dimer may be elevated in the circulation in situations involving thrombus formation and degradation. It has high sensitivity and low specificity for the diagnosis of VTE, with a high negative predictive value and a low positive predictive value, making it more suitable for ruling out the diagnosis in cases of low to moderate suspicion. In cases of high suspicion of VTE, the utility of D-dimer may be questionable.

Since D-dimer is a product of thrombus degradation, specifically the final product of fibrin breakdown, it becomes detectable as soon as the endogenous fibrinolytic system starts acting against thrombus formation. Its measurement can be highly valuable in cases where VTE suspicion is low (Wells score = 1) for screening purposes. Remember that its negative predictive value is high, but its specificity is low. In patients with a high pre-test probability according to the scores, a D-dimer level below 500 ng/mL has a negative predictive value of 92%, indicating low chances of VTE in patients with levels below this threshold.

The diagnostic accuracy of the Wells score varies depending on the type of patient or population to which it is applied (outpatient vs. hospitalized), the extent of thrombosis (proximal vs. distal), and the diagnostic probability (low vs. moderate vs. high). This accuracy is higher in patients with proximal DVT, with a high probability score (>2), who are seen in an outpatient setting.

Therefore, D-dimer cannot be used to exclude VTE without a pre-test evaluation. In cases where the Wells score is low (equal to 1) and D-dimer is negative, VTE can essentially be ruled out. However, in cases where there is a high probability of PE or DVT, it is justified to request a CT angiography or Doppler ultrasound, respectively, without the need for prior D-dimer testing.

Doppler ultrasound is currently the diagnostic test of choice for DVT, with a sensitivity of around 96% and specificity between 98% and 100%. It has the advantage of being a non-invasive test with no contraindications in principle.

Findings suggestive of DVT include non-compressibility of the vein, absence or alterations in flow within the vein, direct visualization of the thrombus, and vein dilation. Thrombosis can present as acute, acute-chronic, or as post-thrombotic changes. Acute thrombus appears deformable under compression, associated with a dilated vein and central location. Chronic thrombus is more rigid and less deformable under compression with the transducer, potentially appearing hyperechoic with a calcified appearance. Over time, partial or total recanalization may occur, with wall thickening and synechiae inside, and the vein's caliber may be normal or even decreased.

Alternative imaging modalities include venography, CT angiography, and magnetic resonance imaging (MRI), which can be used in cases where Doppler ultrasound does not provide sufficient clarity, and there is a high suspicion.

Venography (phlebography), still considered the gold standard for DVT diagnosis, has fallen out of favor due to factors such as the need for contrast, the requirement for a surgical or hemodynamic setting,

and contraindications in patients with chronic kidney disease or contrast allergy.

MRI and contrast-enhanced CT can also be used to diagnose DVT, especially proximal DVT in the iliac veins and inferior vena cava, with or without suspected PE.

Pulmonary angiography, considered the gold standard for PE diagnosis, has also fallen out of favor for similar reasons as venography and has been replaced in practice by contrast-enhanced CT pulmonary angiography, which has become the test of choice.

In positive cases of PE, CT angiography shows filling defects in the pulmonary arteries in the affected segments, confirming the diagnosis. A negative CT angiography, in a patient with low clinical probability, is sufficient to rule out PE. Conversely, a positive scan in a patient with high clinical probability confirms the diagnosis.

Magnetic resonance angiography of the chest, like CT angiography, allows for the evaluation of pulmonary arteries and offers some advantages, such as the absence of radiation and the use of gadolinium as a contrast agent,

which is beneficial for patients allergic to iodine contrast. However, there are disadvantages, including higher cost, longer exam duration, lower spatial resolution, greater complexity, limited availability, and more difficulty in monitoring critically ill patients inside the machine, which has a strong magnetic field.

Chest X-rays can be useful in some cases, primarily in assisting with differential diagnoses, although they may not show abnormalities in cases of PE. When present, the changes are often nonspecific and include infiltrates, diaphragmatic dome elevation, and small pleural effusions. Some typical signs may be present, such as "Hampton's hump," which corresponds to a pulmonary infarction area represented by a wedge-shaped peripheral opacity just above the diaphragm. Another characteristic sign is the "Westermark sign," which is the occlusion of the lobar and segmental artery, causing an area of oligemia and reduced pulmonary markings.

The ECG can show changes compatible with signs of right ventricular overload, such as T-wave inversion in leads V1 to V4, a QR pattern in V1, right bundle branch block, and the S1Q3T3 pattern

However, these patterns are generally more common in severe cases, while in milder cases, only sinus tachycardia may be present.

Pulmonary scintigraphy, although a reliable test, has become less common with the advent of contrast-enhanced CT, which is a faster test and not always available for PE diagnosis.

In practice, pulmonary scintigraphy is defined as a single exam with different combinations, including isolated perfusion study, pulmonary perfusion scintigraphy, and inhalation/ventilation scintigraphy. Its primary indication is to determine the probability of PE, but it also has other common indications in practice, such as evaluating lung transplants, quantifying lung function before surgery for lung tumor removal, assessing the presence of bronchopleural fistulas, evaluating parenchymal lung disorders, and assessing pulmonary hypertension as a cause.

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TREATMENT

TREATMENT

The treatment of VTE aims not only to address the disease itself but also to prevent more severe complications and a possible fatal outcome. Therefore, the importance of accurate diagnosis and assertive treatment cannot be overstated. Additionally, having a thorough understanding of therapeutic options enhances patient safety, as medications available for VTE can carry some risks, primarily related to bleeding episodes.

The cornerstone of VTE therapy is anticoagulants, whether administered parenterally or orally. Regardless of the route of administration, several factors will directly influence the choice of the drug to be prescribed, such as pharmacokinetics, pharmacodynamics, patient comorbidities, drug availability, the medical team's familiarity with the drug, ease of antagonism in case of side effects, medication cost, and patient preference.

For parenteral use, available options include heparins—either unfractionated heparins, which act as thrombin inhibitors and are generally administered intravenously, or low molecular weight heparins, which are administered subcutaneously and work by inhibiting thrombin and factor Xa in the coagulation cascade. Another less commonly used parenteral option is fondaparinux, an ultra-low molecular weight heparin that functions as a synthetic inhibitor of factor Xa. Parenteral treatment is generally reserved for hospitalized patients or specific groups where oral anticoagulants are contraindicated, such as during certain periods of pregnancy.

Oral anticoagulants (OACs) are the most commonly used drugs in VTE treatment today, especially in less complicated cases, due to their ease of administration and other advantages. The first OACs to be successfully used in clinical practice were coumarins (warfarin), which inhibit vitamin K-dependent coagulation factors (II, VII, IX, and X) and also the anticoagulant proteins C and S. The major inconvenience of these OACs is the need for frequent laboratory monitoring, with periodic blood draws

(to monitor PT and INR) and their significant interaction with various medications and even some foods that can impact their pharmacological action, either increasing or decreasing their efficacy.

With the advent of novel oral anticoagulants (NOACs) and their widespread use over the past decade, outpatient treatment has become safer, with lower rates of hemorrhagic complications. Among the NOACs, there are two main groups: factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct factor IIa (thrombin) inhibitors (dabigatran).

Thrombolytic therapy (t-PA, streptokinase, urokinase), administered either via catheterization or systemically, is an alternative for some specific cases of thrombosis or embolism where the severity of the situation prevails. Ideally, this should be done within the first 14 days. In cases of pulmonary embolism, the main indications for thrombolytic use are hemodynamic instability, massive embolism, and right ventricular dysfunction. For DVT, thrombolysis may be indicated in patients with proximal or complicated thrombosis, aiming for early recanalization and reducing the incidence of post-thrombotic syndrome, which significantly impacts patients' quality of life.

It is important to note that the use of thrombolytics significantly increases the risk of bleeding, and their indication should always be carefully evaluated based on the risk-benefit ratio.

In patients with lower limb venous thrombosis who have contraindications to anticoagulant treatment, the implantation of an inferior vena cava filter is indicated to prevent the most feared complication: pulmonary embolism. The implantation of this device is performed through the catheterization of a deep vein, with the filter being released into the vena cava under fluoroscopic guidance.

There is also the possibility of temporary filters that are retrievable and can be removed after a specified period.

Besides contraindications to formal anticoagulation, there are other absolute and relative indications for filter implantation.

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PREVENTION

PREVENÇÃO

Given that VTE has a significant mortality rate and is highly preventable, implementing prevention strategies, especially in high-risk patients, can have a profound positive impact on morbidity and mortality. Among the most susceptible patients are those in states of immobility, those with a diagnosis of active cancer, and hospitalized patients, whether for medical or surgical reasons. For hospitalized patients and/or those undergoing surgical procedures, several scores are available to help stratify risk and implement appropriate prophylaxis (mechanical or pharmacological).

A systematic review analyzing 33 randomized controlled trials demonstrated the safety of pharmacological prophylaxis, with significant bleeding observed in only 3% of cases. Several randomized controlled trials have confirmed the efficacy of preventing VTE using low molecular weight heparin in surgical patients, reducing fatal thromboembolic events by up to 63%.

The Padua score (for medical patients) and the Caprini score (for surgical patients) assist in risk stratification and decision-making regarding individualized VTE prophylaxis. Therefore, measures such as the use of graduated compression stockings, intermittent pneumatic compression, early ambulation, and the administration of anticoagulants in the correct dose should always be adopted rationally to ensure that VTE prevention is safe and effective without exposing the patient to unnecessary risks.

VTE prophylaxis should be instituted in hospitalized medical patients, as they have a 20-fold higher risk of developing the disease compared to outpatients, particularly when bedridden. Patients over 40 years old, with reduced mobility for more than 3 days, and at least one risk factor should be stratified for preventive measures. The most commonly used tool for this is the Padua Score, where patients are classified as high risk when >4 and low risk when ≤4.

For surgical patients, it is recommended that every hospital develops a strategy for the prevention and management of VTE, as the risk is even greater than in most medical patients and can persist on average for 12 weeks after surgery and, in some specific cases, up to 1 year.

When implementing VTE prophylaxis in surgical patients based on the Caprini score, three main points should be considered for risk stratification: age, duration of surgery, and associated risk factors.

Regardless of the condition that led a patient to be hospitalized, VTE prophylaxis strategies should be taken very seriously, as the impact of prevention on mortality is well-proven and documented.

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FINAL CONSIDERATIONS

FINAL CONSIDERATIONS

This e-book aims to contribute to the learning of venous thromboembolic disease for medical students in their professional cycle. By using accessible language tailored to medical practice, the material seeks to link the basic knowledge acquired during medical school with new, updated information, assisting in the development of clinical reasoning and positively impacting the training of general practitioners.

Furthermore, due to the importance of the topic addressed, this product aims not only at learning about VTE but also at combating this disease through the dissemination of medical knowledge. The information acquired through this e-book is intended to promote the prevention of complications by understanding prophylactic, diagnostic, and therapeutic measures.

Finally, the use and dissemination of this material open up a range of future possibilities for the development of new resources aimed at spreading knowledge about VTE among medical students, enabling the continuous acquisition of up-to-date knowledge related to the subject.

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