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Emerging Issues in Deep Vein Thrombosis; (DVT) in Liver Disease and in Developing Countries

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1. Introduction

This chapter addresses a new and emerging aspect of health in developing countries – one that poses a serious and growing burden on individuals, health systems, and economies of poor countries but is largely preventable. Deep Vein thrombosis (DVT) is a major medical, social and economic problem in developed countries, but in developing countries scanty information is available. Blood clots such as thrombus in a deep vein in the lower limb is the most serious unexpected killer of hospitalized patients in developed countries and over the years this has led to elaboration of numerous strategies directed towards reducing the risks of formation of such thrombi and treating them when they occur. This area has been covered extensively in the literature emerging from developed countries, and little is known about the pattern and scale of problem in developing countries.

Another area that will be covered in this chapter relates to hypercoagulation in chronic liver disease which is poorly understood till recently. Because of the relatively uncommon occurrence of overt clinical thrombosis in patients with liver disease, and the complexity of the haemostatic mechanism, in addition to the fact that clinicians often perceive that these patients are at a reduced risk for venous thromboembolism, DVT in liver disease is an understudied problem. In this chapter, we aim to discuss DVT from two aspects; DVT in liver disease, and DVT in developing countries.

2. Deep vein thrombosis in liver disease

Chronic liver diseases in the United States account for 400,000 hospitalizations and 27,000 deaths (Kochanek et al., 2004, Kozak et al. 2005). This area needs to be revisited with respect to DVT in liver disease, where viral liver disease is more common in developing countries than in developed countries (Williams, 2006.). Patients with advanced liver disease (a failing liver) display a complexity of haemostatic abnormalities often occurring concurrently including coagulopathic, hypercoagulable, and hyperfibrinolytic disorders and increased platelet activation. Recent literature has revealed that hypercoagulability plays an important role in many aspects of acute and chronic liver disease (Nieuwdrop et al. 2005, 2004). The resulting clinical state is determined by which component of these complex haemostatic mechanisms predominates.

2.1 Pathophysiology of the coagulation mechanism

Under normal conditions, the blood circulates freely within the vascular system. However, when blood escapes to extravascular sites after blood vessel injury or it becomes pathologically challenged, haemostasis may be activated ending in the formation of blood (fibrin) clot. This process is finely regulated by positive and negative feedback loops that control fibrin clot formation.

For many decades the accepted blood coagulation mechanism has been based on the concept of the coagulation cascade model that describes the interactions of the coagulation factors along two pathways: the intrinsic pathway which is triggered by the contact of blood with a foreign surface, and the extrinsic pathway which is triggered by exposure of the blood to the transmembrane receptor tissue factor (TF) which binds to clotting factor VIIa to form TF/FVIIa complex. Both pathways meet at the level of clotting factor X after which the common pathway progresses until the generation of the thrombin and the formation of fibrin clot. However, while the cascade model delineates the interactions between the coagulation proteins and provides a framework for interpreting the common screening coagulation tests (particularly the PT and the APTT), it is gradually been realized that the cascade model suffers from many limitations, as it fails to explain convincingly how hemostatic activation occurs *in vivo*. For example, this model cannot explain why hemophiliacs bleed when they have an intact factor VIIa/TF "extrinsic" pathway.

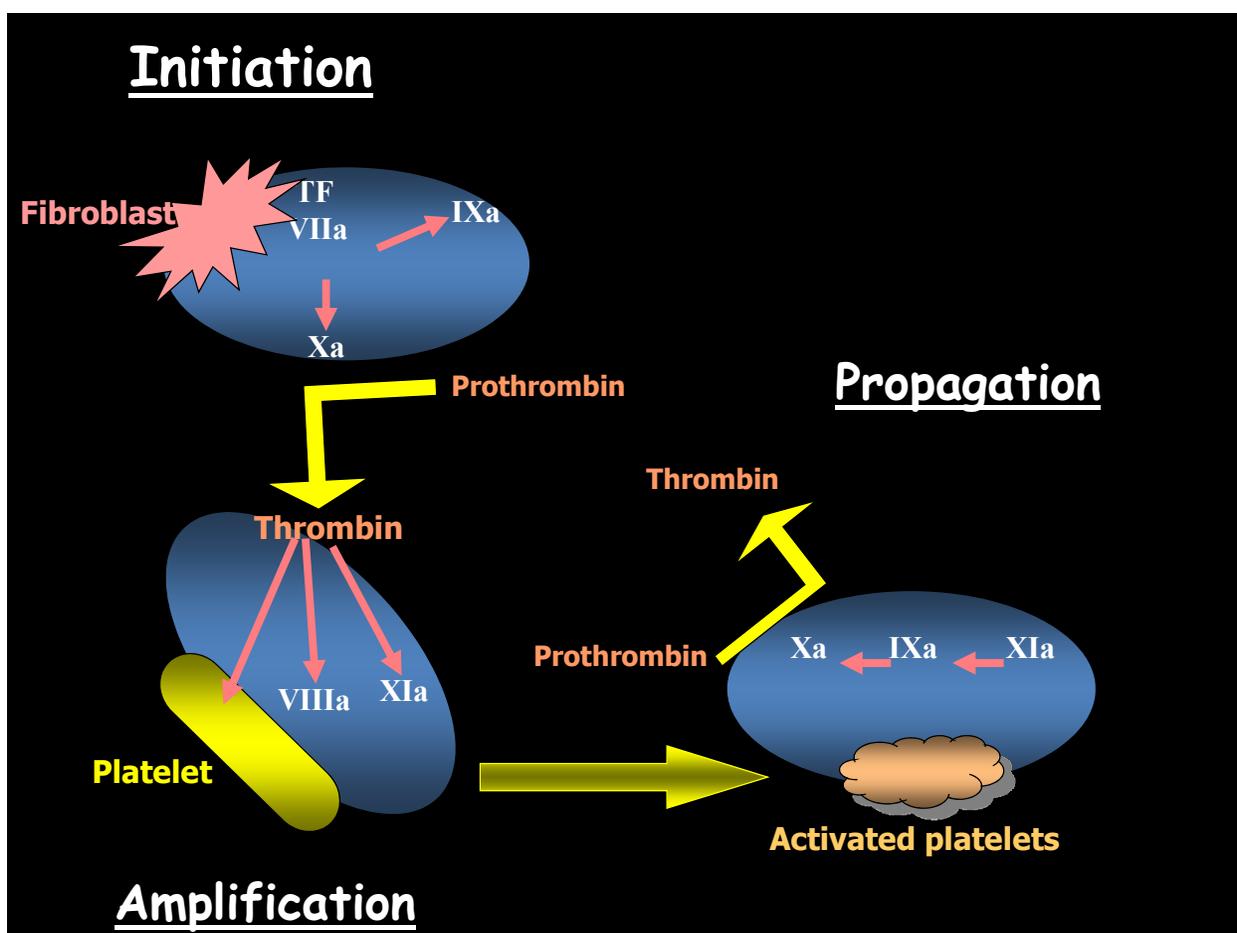


Fig. 1. Cell-based model of the mechanism of blood coagulation

The classical cascade model of the coagulation cascade is being replaced by the new, cell-based model of coagulation (Roberts et al., 2006) (Fig. 1), which emphasizes the interaction of coagulation proteins with cell surfaces of platelets, subendothelial cells and the endothelium. According to this model the coagulation is initiated (The Initiation Phase) by the formation of a complex between tissue factor (TF) exposed on the surface of fibroblasts as a result of a vessel wall injury, and activated factor VII (FVIIa), normally present in the circulating blood. The TF-FVIIa complexes convert FX to FXa on the TF bearing fibroblasts. FXa then activates prothrombin (FII) to thrombin (FIIa). The next phase is the Amplification Phase in which this limited amount of thrombin activates FVIII, FV, FXI and platelets, on the surface of blood platelets. Thrombin-activated platelets change shape, and as a result will expose negatively charged membrane phospholipids, which form the perfect template for the assembly of various clotting factors and full thrombin generation involving FVIIIa and FIXa (The Propagation Phase). According to this cell-based model the tissue factor (TF) extrinsic pathway is the principal cellular initiator of normal blood coagulation in vivo (Mackman et al. 2007), and the major regulator of haemostasis and thrombogenesis, with the intrinsic pathway, playing an amplification role.

2.2 The role extrinsic pathway in thrombosis

From the above account, it is clear for clotting to occur blood must be exposed to tissue factor. Therefore for thrombosis to set such exposure will happen when the blood vessel is injured and blood comes in contact with variety of cells that express TF, in particular monocytes and neutrophils. Endothelial cells also express TF mostly due to binding TF-expressing microparticles (MPs- see below) (Schwartz et al. 2006). More prominence has recently been given circulating TF-positive microparticles (MPs) (Morel et al. 2006). These are small membrane fragments released from activated or apoptotic vascular cells (Rauch et al., 2007).

There is strong evidence to show that TF-positive MPs contribute to thrombosis in patients with cancer (Rauch et al., 2007, Tesselaar et al., 2007), cardiovascular disease (Misumi et al., 1998), and sickle cell disease (Shet et al., 2003). Many cell types can generate circulating TF-positive MPs including leucocytes, endothelial cells, platelets and vascular smooth muscles and these MPs can be recruited to a thrombus and enhance its growth in both arterial and venous thrombosis (Schwartz et al. 2006).

2.3 Pathophysiology of coagulation mechanism in liver disease

In case of severe liver disease the protein levels that are synthesized in the liver are reduced as the synthetic capacity is lost. Thus, levels of both pro- and anticoagulant proteins decrease as liver disease progresses. A relatively balanced reduction in pro- and anticoagulant activity does not result in a net hyper- or hypocoagulable state until the loss of liver synthetic capacity is severe. However, the ability of the haemostatic system to maintain haemostasis when stressed is progressively reduced. Thus, the balance between bleeding and thrombosis becomes increasingly precarious as protein synthetic capacity is lost.

In addition, the important role of endothelial function in maintaining haemostatic balance means that local endothelial dysfunction can lead to the development of a hypercoagulable state at one anatomic site. Thrombotic complications can be seen in the portal and

mesenteric systems (Mammen et al., 1992), hepatic veins (Singh et al., 2000), and peripherally in the extremities with associated pulmonary emboli (Northup et al., 2006). The prothrombotic state may be involved in other sequelae of chronic liver disease, including hepatic parenchymal extinction, fibrosis and portopulmonary hypertension. Thus, a prolonged prothrombin time does not adequately portray the levels of other clotting factors, particularly factors VIII, X and II that can be more than adequate to promote clot formation (Violi et al., 1995). As well, it is known that the coagulation disorders associated with failing liver can induce further hepatic damage, namely, parenchymal extinction. Wanless et al (Wanless et al., 1995) have clearly demonstrated the histopathologic evidence of the secondary hepatic damage caused by circulatory disturbances due to thrombotic occlusion of intrahepatic blood vessels (microvascular thrombosis).

2.4 The prevalence of deep vein thrombosis in liver disease

Deep vein thromboses in the lower extremity are common in the general medicine population without liver disease and range from 4% to 12% in inpatients (Anderson et al., 1991, Stein et al., 2002). Patients with cirrhosis share many of the same risk factors as hospitalized general medicine inpatients, including prolonged immobility, obesity, recent surgical procedures and malignancies. The presence of anticardiolipin and antiphospholipid antibodies have also been documented in patients with cirrhosis (Violi et al., 1994) and hepatitis C (Prieto et al., 1996). Hyperfibrinolysis, perhaps related to persistence of tissue plasminogen activator, is also prevalent in decompensated cirrhosis (Gunawan et al., 2006). It is not commonly symptomatic that DVT events may occur in patients with liver cirrhosis despite the coagulopathy of liver disease and clinical experience suggests this is the case. Several studies have shown lower levels of antithrombin, protein C and protein S in cirrhosis patients compared with controls (Mammen EF et al., 1992, De Caterina et al., 1993, Vukovich et al., 1995, Walker et al., 1990, Zurborn et al., 1988). Indeed, the diminution in the circulating levels of these inhibitors was noted in the early stages of liver disease and well before the setting of its chronic stages as in liver cirrhosis (Al-Ghumlas et., 2005, Abdo et al., 2010),

The literature is sparse in the area of clinical DVT in cirrhosis and is limited to case reports and a single case-controlled study (Ben Ari et al., 1997) comparing hospitalized cirrhotic patients with and without DVT. In this retrospective study, a new DVT or PE was diagnosed in appropriately 0.5% of all inpatients with documented cirrhosis despite 21% of these patients being on some form of DVT prophylaxis. While the rate of VTE is lower than expected in the general medicine population, these data show that patients with liver cirrhosis are not immune to VTE. It is plausible that this underestimates its true incidence. This could be explained as symptoms of VTE in the decompensated liver cirrhosis patients, particularly edema and dyspnea are common and not specific. Diagnosis requires a high index of suspicion and accurate radiologic testing methods.

2.5 Clinical presentation

The symptoms of DVT in the decompensated cirrhotic patient, edema, and dyspnea are common and not specific; those patients have similar risk factors as medical inpatients. Patients with liver disease can present to medical services with complaints of leg edema, leg pain dyspnea, and abdominal pain.

2.6 Diagnostic and treatment challenges

Diagnosing DVT in patients with liver disease need high level suspicion, presence of laboratory investigation such as D-dimer and radiological procedure of Duplex ultrasound; thus elevation of coagulation markers such as the prothrombin time and partial thromboplastin time does not safeguard against thrombotic events. Serum albumin level was independently associated with the occurrence of thrombosis (Ben Ari et al., 1997, Senzolo et al., 2009).

2.7 DVT prophylaxis in liver disease

Current guidelines from American College of Chest Physicians (ACCP) DVT prophylaxis do not specifically comment on the advanced liver disease patients' population (Senzolo et al., 2009). The lack of specific guidelines is because of the perceived risk of bleeding complications, sense of auto-anticoagulation, impaired laboratory tests, and most important lack of clinical trials to support the practice of routine use of DVT prophylaxis in liver disease/cirrhosis and its safety, particularly the risk of bleeding is unknown. Recently two studies (Senzolo et al., 2009, Bechman et al., 2010.) found that the prophylactic use of LMWH in patients with cirrhosis and who are at high risk of thrombosis, to be safe from the risk of bleeding. Actually Bechman et al., 2010 revealed for the first time, to our knowledge, there are apparent decreased efficacy of LMWH in cirrhotic patients, which may indeed argue for studying the appropriate dosing in cirrhotic patients (Bechman et al., 2010).

In a recent study, approximately 76% of the cirrhotic patients included in the cohort received neither pharmacological nor mechanical DVT prophylaxis. No significant differences in the incidence of VTE were observed between the group that received pharmacologic or mechanical prophylaxis and the group that did not receive prophylaxis (Abdulaziz et al., 2011). The utilization of DVT prophylaxis was suboptimal.

Until the risks and benefits of VTE prophylaxis are established in this particular population, the VTE prophylaxis cannot be withdrawn in the cirrhotic population at present time. (Senzolo et al., 2009).

3. Deep vein thrombosis in developing countries

Deep vein thrombosis is a preventable disease and the incidence of VTE is 1-3 per 100 per year (Nordström et al., 1992; Anderson et al., 1991; Oger et al., 2000; Cushman et al., 2004,). DVT is a significant cause of morbidity and mortality and without prophylaxis, the risk of a DVT event is especially high in patients admitted to medical orthopedic surgery wards (Geerts et al., 2008), with an incidence of venographic DVT without prophylaxis estimated at 40% to 60% (Geerts et al., 2008). Given its silent nature; the incidence, prevalence, morbidity and mortality rates of DVT are probably under-estimated in developing countries. Although most patients survive DVT, yet serious and costly long-term complications may occur; almost one-third of patients will suffer from venous stasis syndrome (postphlebotic syndrome) (Prandoni et al., 1996). DVT is a major burden on US healthcare systems: estimates put costs at nearly \$500 million per year (Hawkins, 2004).

3.1 Scale of DVT problem in the developing countries

DVT in developed countries is considered a public health problem and over the years this has led to elaboration of numerous strategies directed towards reducing the risks of DVT.

Given this to be the situation in the developed countries, the the magnitude of the problem would be much lower in the developing countries. Indeed many population studies that are carried in Western developed countries documented the lower incidence of VTE in Asians and Hispanics compared to Caucasians (Kearon 2001, White et al 2009).

Although there is strong evidence that the prevalence of venous thrombo-embolism (VTE) varies significantly among different ethnic/racial groups, the genetic, physiologic and/or clinical basis for these differences remain largely undefined (White et al ., 2009).

Identifying the scale of DVT in developing countries is difficult due to scanty and conflicting available published literature on the scale of the problem, the diagnostic tools, management and treatment challenges facing these countries. Most published information on the DVT was generated from small hospital-based studies that documented DVT as a significant complication of orthopedic surgery particularly total knee arthroplasty (Chung et al 2010, Ko et al. 2003, Leizorovicz et al 2005, Sen et al 2011, Sen et al 2011), and general hospital patients (Ogeng'o et al 2001, Angchaisuksiri et al 2007, Sakon et al. 2006, Lee et al. 2009). Essentially all these and other similar studies advocated the importance of thromboprophylaxis to avoid the risk of VTE.

As to population studies very few could be identified and almost all from Asian Far Eastern countries particularly China and Korea. In one study from Korea the incidence of VTE, DVT and PE per 100,000 individuals was found to be 8.83, 3.91 and 3.74 in 2004 and increased to 13.8, 5.31 and 7.01 in 2008 (Jang et al 2001). Another recent study from Hong Kong documented an annual incidence of of VTE at 16.6 events per 100,000 populations (Lui et al 2002). Another Chinese study reported the incidence of DVT and PE of 17.1 and 3.9 per 100,000 populations (Cheuk et al 2004). The incidence of DVT in all three studies is almost one tenth that reported from developed counties; yet the problem of DVT remains to be a health problem that clinicians should be aware of.

3.2 Challenges of DVT In developing countries

3.2.1 Health disparity in the developing world

There is remarkable disparity in standards of the health care among developing countries, especially the percentage of the Grand National Product that is expended in health care. Also, when comparing developed to developing countries, some countries like Saudi Arabia, Egypt, Jordan and the UAE could take the lead: Egypt (5.8%), Saudi Arabia (4%), Pakistan (2.4%) and India (4.8%) have limited total expenditure on health, compared to the United States (15.2%), Switzerland (11.5%), France (10.1%) and Norway (10.3%) (WHO Health Report, 2006). Such disparity shows up as unequal distribution of healthcare personnel and deficiency in training programs in the developing world. This is also reflected on the life expectancy and disease outcome and survival in these countries.

3.2.2 Registries

In reviewing the available evidence on the epidemiology of deep vein thrombosis (DVT) in the developing countries, it is quite clear that there are few on-going registries that track data on patients with DVT. Most of those registries are hospital-based rather than national. For example in Saudi Arabia there is the Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry (Saour et al., 2009), which is considered the only registry in Gulf Region and

perhaps the Middle East. In developing countries there is very scanty and non-conclusive data on the prevalence, incidence, risk factors, genetic predisposition, distribution of DVT occurrences among different age groups and gender, and the burden of DVT on different patient groups (e.g. post-surgical, pregnancy etc...). Most importantly, how physicians manage DVT is also unknown and no cost-effective analysis is available on the current treatment regimens deployed in these countries. Such registry for DVT should include demographic data and extensive medical history (past and present). Detailed information on environmental, lifestyle and occupational factors could help identifying certain groups who are at increased risk of developing DVT or its complications. There is also need to accumulate laboratory data which should include blood group, factor VIII, inherited thrombophilic defects (such as factor V Leiden and prothrombin mutations), fibrinogen level, as well as routine laboratory investigations. Screening for inherited thrombophilia and other genetic diseases that predispose to DVT is crucial and has gained popularity worldwide. The available data on the prevalence of thrombophilic risk factors for VTE, particularly factor V Leiden, prothrombin G20210A, mutations C677T methylenetetrahydrofolate reductase and hyperhomocysteinaemia) in developing countries is scanty but agree on their rarity and much lower prevalence than in developed countries (Jun et al 2006, et al 2002, Lim et al 2004, Omar et al 2007).

3.2.3 Epidemiology

The burden of DVT in the developing world is unknown due to lack of documentation and large-scale research projects aiming at identifying the different epidemiology aspects. Some of the developing countries (Saudi Arabia, United Arab of Emirates and the rest of the Arab Gulf countries), have the financial resources to setup such registries. However, setting up registries requires substantial training to the current and future personnel who are working fulltime in maintaining them. Policymakers, represented by the governments, academic medical centers and, most importantly, local and regional funding agencies, must work together in order to consider emphasizing DVT as a public health problem so that the appropriate increasing proportion of public health resources is reallocated to address DVT and its related issues.

3.2.4 The cost and value of pharmacoeconomics research

Registries will not only allow tracking DVT in terms of its epidemiology, but also how much it burdens each country's economy. Pharmacoeconomic analysis is of great value in the evaluation of the cost of medical care. For example, cost-identification analysis seeks to identify the cost of providing the treatment of the disease. Cost-minimization analysis seeks to identify the least expensive alternative intervention to get the same outcome after treating the disease. Most importantly, cost-of-illness analysis estimates the total financial burden of DVT or its associated disability (e.g. reduced working hours, sick days, less life-expectancy etc...) to the country. This is done by estimating the total cost of diagnosing DVT, its management and the DVT-associated lost productivity. Cost-benefit analysis evaluates one or more treatment regimens in terms of pure currency expressions (e.g. dollars). This will allow the governments to identify which diseases cost higher. For example, in this form of analysis, we can compare the cost of DVT awareness, prevention and treatment to the cost of chronic kidney disease. Such analysis guides the policymakers to identify the top ranked diseases affecting the economy and allocates more dollars to combat them.

3.2.5 Awareness and education of the public

We believe that intensive awareness and educational campaigns supported by the media and endorsed by the governments will contribute in limiting the DVT problem. For example, school teachers and cashiers should be advised, and allowed, to move around during their working hours since their job entails long standing hours. Educational initiatives in the airports and airplanes in the form of brochures or brief videos are encouraged to increase travelers' awareness. With such efforts, it might be expected that there would be a reduction in the number of individuals who develop DVT which, in turn, might reduce the number of patients requiring treatment and follow up as post thrombotic syndrome long run.

3.2.6 DVT diagnosis

The use of pretest probability scoring system such as Geneva score (Kelly et al., 2003), Wells score (Wells et al., 1997) to diagnosis DVT is considered commendable efforts towards early diagnosis. This could be germane to the developing countries in reducing the economic cost that may have the impact on the scale of DVT. This will also help the researchers and clinicians, policymakers to make proper assessment of the magnitude of the problem, management, and prevention strategies.

3.2.7 Clinical and research training programs

We believe that the lack of training programs in clinical hematology in the developing countries is contributing to the problem of misdiagnosing and under-diagnosing of DVT. Unlike the Western countries, such training programs are limited to the medical schools which may not meet the need of any country to well-trained hematologists. It is important that special emphasis on undergraduate medical education, by inclusion of management and prevention strategies in the medical curriculum, will increase the early reporting of DVT by different medical specialists. On the other hand, training programs should be developed to train the allied health professionals (e.g. nurses, technicians etc...) on aiding the clinicians in diagnosing DVT. Establishing a strong research infrastructure in terms of highly trained and qualified fulltime research personnel, research facilities and budgets will help to bridge the knowledge gaps in DVT in developing countries.

3.2.8 Cultural and social issues

There are some cultural and social issues that may contribute to the underreporting of the DVT in the developing countries. Having a chronic disease may represent a stigma. Being diagnosed with DVT is considered a social disability. Women usually hide having any kind of disease especially if it is DVT-related pregnancy which may affect her ability of childbearing.

4. Conclusion

In conclusion, we believe that addressing DVT as a regional public health problem in the developing countries should take a multi-dimensional approach targeting the epidemiology of DVT and implementation of cost-effective preventive and therapeutic programs.

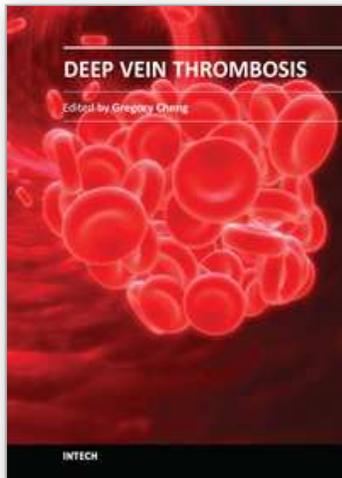
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This book provides a comprehensive review of deep vein thrombosis. There are chapters on risk factors for DVT, post thrombotic syndrome and its management, vena cava malformation as a new etiological factor and thrombosis in the upper limbs. DVT is usually seen in patients undergoing major surgeries. The guidelines for thrombo-prophylaxis in orthopaedic patients, radical pelvic surgeries, laparoscopic operations and risks versus benefits in regions with a low prevalence of DVT are thoroughly addressed. Cancer and its treatment are recognized risk factors for VTE and extended prophylaxis in ambulatory cancer patients is reviewed. The role of imaging and endovascular therapies in acute DVT, hypercoagulability in liver diseases and the challenges in developing countries are discussed.

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