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1. Introduction

Heparin-induced thrombocytopenia (HIT) is an immune-mediated response to heparin administration that causes thrombocytopenia and a prothrombotic state. Heparin is the most commonly used anticoagulant drug for the prevention and treatment of thromboembolic diseases in hospitalized patients. Heparin exists in two main forms, pure unfractionated heparin (UFH) and low molecular weight heparin (LMWH), which is derived from UFH. Though HIT is relatively rare, occurring in less than 5% of patients receiving UFH and less than 1% of patients receiving LMWH, it has the potential to cause significant morbidity and mortality. The main complication of HIT is thrombosis, most commonly deep vein thrombosis (DVT) or pulmonary embolism (PE). More rarely HIT can manifest as occlusion of a limb artery, acute myocardial infarct, stroke, a systemic reaction or skin necrosis. In the current chapter the topic of HIT will be reviewed in terms of its pathophysiology, diagnosis, and treatment.

1.1 Clinical Vignette: Patient S-B

S-B is a 48-year-old male who was admitted to the orthopedics service for surgical repair of a right acetabular fracture resulting from a fall. He had no significant past medical history. His course was complicated by an ileus. He was given enoxaparin for thromboprophylaxis starting on day 2 of admission. During his hospital stay, he developed a pulmonary embolus and atrial fibrillation and the dose of enoxaparin was increased. An IVC filter was also placed. His platelet count dropped from 278K/uL on admission to a low of 88K/uL on hospital day 10. HIT antibody was positive. Enoxaparin was discontinued and lepirudin was started. Platelet count began improving by the next day and was 190K/uL two days after starting lepirudin. He was transitioned to warfarin. A PICC line was placed for parenteral nutrition as his ileus had not resolved.

Several days later, the patient suddenly developed shortness of breath, chest pain, nausea and fever of 102°F. His heart rate increased to 130; he was normotensive. An arterial blood gas revealed metabolic acidosis and hypoxemia; his lactate level was elevated. Chest x-ray showed no infiltrates and a CT pulmonary angiogram (CTPA) was negative for infiltrates, pulmonary emboli and other pathology. EKG showed sinus tachycardia. Antibiotics were begun for possible sepsis. Platelet count was found to be 114K/uL compared to 231K/uL the previous day. Review of his chart revealed that the patient had received heparin flushes of his PICC line as part of a standing protocol. Heparin flushes were discontinued and lepirudin was restarted. Over the next several hours his fever, tachycardia, and hypoxemia improved. His lactate level normalized and platelets rose to 160K/uL by the following morning. All cultures were negative and antibiotics were discontinued.
2. Pathophysiology

Heparin is a negatively-charged, highly sulfated glycosaminoglycan that occurs naturally in the body. It was discovered nearly one century ago (Howell & Holt, 1918) and shortly thereafter was used in the medical profession for thromboprophylaxis in post-operative patients (Crafoord, 1936). Amongst the qualities that made it an attractive option for physicians were its immediate onset of action and its short half-life. During the first three decades of its use in the medical field, case reports and series of patients developing thrombosis while on heparin began to emerge in the literature, a phenomenon known as HIT (e.g. Weismann & Tobin, 1958; Roberts et al., 1963). Over the last several decades much has been learned about heparin and the mechanisms that are responsible for this disorder.

Physiologically, two types of thrombocytopenia due to heparin exposure have been described. Non-immune heparin-associated thrombocytopenia, historically referred to as HIT type 1, describes a response that is self-limiting and rarely causes major complications. Non-immune HIT occurs in 10% to 30% of patients who receive heparin and typically emerges within 4 days of exposure (Jang & Hursting, 2005). Platelet counts do not normally fall below 100K/µL. Heparin use does not need to be discontinued and no treatment is needed (Chong, 2003).

Currently the term HIT is used to denote what has been historically called HIT type 2. HIT occurs when, following heparin administration, platelet factor 4 (PF4) binds to heparin to form heparin/PF4 complexes. The body identifies these complexes as abnormal and, in response, develops antibodies. Specifically immunoglobulin G (IgG), M (IgM) and/or A (IgA) antibodies are formed. IgG is pathogenic, and binding of the IgG antibodies to the heparin/PF4 complexes results in platelet activation and aggregation. This causes thrombin generation, resulting in thrombotic events. Activated platelet aggregates are removed prematurely from circulation, which leads to development of thrombocytopenia, the main criteria for diagnosis of HIT (Warkentin et al., 1994a; Untch et al., 2002). The heparin/PF4 antibodies (also known as chemokine CXCL4) are typically activated within 5-14 days of heparin exposure, though delayed-onset cases have been reported (Warkentin & Kelton, 2001a). In patients who have a recent history of heparin use, however, significant platelet activation can occur more rapidly after reintroducing a heparin-containing product (Warkentin & Kelton, 2001b). This may be because HIT antibodies are transient and can remain in the body for up to four months after withdrawal of heparin (Lubenow et al., 2002).

Though the exact mechanisms of action are unclear, endothelial cells and monocytes also seem to play a role in the procoagulant state associated with HIT (Blank et al., 2002; Pouplard et al., 2001; Rauova et al., 2010; Arepally & Mayer, 2001). Many processes still remain unexplained in HIT, including the inability of some anti-heparin/PF4 IgG molecules to cause platelet activation (Warkentin, 2005) and the role of individual biological differences in predisposing to development of the disease. There is evidence that the length of the heparin molecule chain may positively correlate with the potential for HIT. Since LMWH’s are formed from smaller molecules, this could explain why there is less immunogenic potential in these derived forms of heparin (Gruel et al., 2003). Furthermore, there may be a role of other glycosaminoglycans that are found on the surface of platelets, which may cross-react with heparin/PF4 antibodies and more directly cause thrombus formation (Rauova et al., 2006).
3. Clinical features

3.1 Epidemiology
Several factors have been identified as being associated with an increased risk of HIT. At the patient level, HIT has been more frequently reported in females (Warkentin et al., 2006) and in patients over 40 years of age (Stein et al., 2009). Patients on UFH have a higher likelihood of developing HIT than those on LMWH (Martel et al., 2005). Dosage is also an important factor; patients receiving therapeutic doses may be more likely to develop clinical manifestations of HIT than those receiving prophylactic doses (Dager & White, 2003). Patients receiving thromboprophylaxis with UFH for six or more days have a higher incidence of HIT than those receiving it for shorter periods (Martel et al., 2005; Smythe et al., 2007). Furthermore, the preparation type seems to influence risk; bovine UFH is more likely to cause HIT than porcine UFH (Green et al., 1984; Bailey et al., 1986; Francis et al., 2003). In general, surgical patients are at a higher risk of developing HIT than medical patients (Warkentin et al., 2006), but there is variation in incidence between surgical types. Since HIT develops secondary to the formation of heparin/PF4 complexes, it would be logical to assume that patients with higher concentrations of circulating PF4 would be at greater risk, including patients undergoing cardiac surgery on cardiopulmonary bypass (Yoon & Jang, 2011). However, the incidence of HIT in these cardiac surgery patients is less than 3% (Warkentin et al., 2000), whereas those who undergo orthopedic surgery, which is associated with less PF4 production, has incidence rates of HIT around 5% (Warkentin et al., 2003). The mechanism underlying this difference is not clearly understood, but evidence from data collected in trauma patients suggests a role of inflammatory processes in the development of heparin/PF4 complexes (Lubenow et al., 2010).

3.2 Timing
Thrombocytopenia secondary to HIT commonly occurs between 5 and 14 days after the onset of heparin therapy. Patients with recent heparin exposure (e.g. within 30 to 100 days) may develop a significant fall in platelets related to HIT more quickly, even within minutes of re-exposure (i.e. rapid-onset HIT) (Warkentin, 2004; Warkentin and Kelton, 2001b). This is likely due to the continued presence of antibodies from previous exposure (Warkentin and Kelton, 2001b; Lubenow et al., 2002). Conversely, there have been cases of HIT where symptoms do not manifest until 10-14 days or more after heparin withdrawal, a phenomenon known as delayed-onset HIT (Warkentin and Kelton, 2001a). This phenomenon is not completely understood. It is known that the anti-heparin/PF4 antibodies can remain in the system for 100 days or more following discontinuation of heparin therapy and that the antibody titers in patients who develop delayed-onset HIT are very high (Rice et al., 2002; Warkentin & Kelton, 2001a). There may be a role of cross-reactivity with other glycosaminoglycans residing on the surface of platelets, thus inducing platelet activation in the absence of heparin (Rauova et al., 2006).

3.3 Degree of thrombocytopenia
In the majority of patients with HIT the platelet count drops below 150K/μL, or falls to less than 50% of baseline. HIT may be overlooked when the platelet count remains above 100K/μL if prior values are not reviewed. The nadir platelet count in HIT typically does not fall below 20K/μL; if such an extensive drop is seen, alternate or additional diagnoses must be seriously considered (Warkentin, 1998). Generally the nadir platelet count in HIT is between 40 and 80K/μL (Greinacher et al., 2005).
3.4 Complications

Thrombosis occurs in 30% to 70% of cases of HIT, depending on the population, and can occur without the presence of significant thrombocytopenia (Warkentin, 2007). Thrombotic events may occur days prior to the onset of thrombocytopenia (Greinacher et al., 2005). In patients who develop a thrombotic event who are either on or have recently completed heparin therapy, the possibility of HIT should be considered (Levine et al., 2006). In addition, it is important to realize that small amounts of heparin, such as those used to perform heparin flushes, can also cause significant manifestations of HIT (Refaai et al., 2007). When HIT is associated with thrombosis approximately 20-30% of cases are fatal and an additional 20-30% result in permanent disability (Greinacher, 1995). DVT (50%) and PE (25%) are the most common thrombotic events related to HIT. Arterial thrombosis, infrarenal aortic thrombosis (Karkos et al., 2011), acute myocardial infarct (Iqbal et al., 2007), cerebral ischemia (Meyer-Lindenberg et al., 1997), limb ischemia (Kreidy & Hatem, 2004), acute adrenal insufficiency (Poulain et al., 2008) and bilateral adrenal hemorrhage (Ernest & Fisher, 1991; Rosenberg et al., 2011) are less common. Skin lesions, which may or may not be necrotic, can be seen at the heparin injection site in 10% to 20% of patients who develop HIT (Jang et al., 2005). Skin lesions appear to be more common in patients with higher levels of platelet-activating IgG (Warkentin, 1996). Despite the presence of thrombocytopenia, bleeding complications related to HIT are uncommon (Selleng et al., 2007).

Systemic or anaphylactoid reactions can rapidly occur after an IV bolus of UFH. In addition to a marked decline in platelet count, patients may develop fever, chills, respiratory symptoms that may simulate a pulmonary embolus (Hartman et al., 2006; Popov et al., 1997), cardiac arrest, gastrointestinal symptoms such as nausea, vomiting and diarrhea, or even neurologic symptoms such as ischemia or transient global amnesia (Warkentin et al., 1994b; Warkentin & Greinacher, 2009). It is important to note that these reactions are due to the immune-mediated response to heparin therapy (Warkentin & Greinacher, 2009); additional cases of anaphylactic reactions due to contaminated or over-sulfated heparins also exist (Liu et al., 2009). This type of systemic reaction is illustrated in the clinical vignette at the beginning of the chapter.

In hemodialysis patients, a unique set of complications may emerge as a result of HIT. For example, there may be clotting of the extracorporeal circuit or failed arteriovenous fistulae. If an IV bolus of UFH or LMWH is given prior to hemodialysis and systemic reactions occur, it is important to consider HIT as a cause (Syed and Reilly, 2009). Increased circuit pressures, formation of a clot in the drip chambers, clotted dialyzer fibers, or an acute thrombocytopenia with at least a 20% decrease in platelet counts may also be suggestive of HIT (Yamamoto et al., 1996).

3.5 Alternative causes

Thrombocytopenia is frequently encountered in critically ill patients and can have a variety of etiologies. ICU patients often receive UFH or LMWH for either prophylaxis or treatment of venous thromboembolic disease or for treatment of a variety of other conditions, such as cardiac ischemia or atrial fibrillation. The question of HIT is therefore frequently raised (Sakr, 2011). However, HIT is actually an uncommon cause of thrombocytopenia in this patient population with an incidence of less than 1% (Crowther et al., 2010; Verma et al., 2003). Some more common causes of thrombocytopenia in critically ill patients include...
Heparin-Induced Thrombocytopenia

sepsis and infection, non-heparin drugs, disseminated intravascular coagulation (DIC), chronic liver disease, immune disorders, and pseudo-thrombocytopenia (Sakr, 2011; Rice et al., 2009). A list of drugs to consider when determining the cause of thrombocytopenia can be found in Table 1. Note that the Table does not include chemotherapeutic agents since most drugs in this class are well-known to cause thrombocytopenia. Serologic confirmation is often delayed for several days and physicians are forced to make decisions based on clinical judgment alone. Therefore, especially in very ill patients, close attention must be given to all possible causes of thrombocytopenia.

4. Diagnosis

Recent data from the CATCH (Complications After Thrombocytopenia Caused by Heparin) registry suggests that less than 10% of patients who develop thrombocytopenia receive a diagnostic evaluation for HIT (Oliveira et al., 2008). Furthermore, many do not receive diagnostic attention for possible HIT until after a thromboembolic event has occurred (Crespo et al., 2009). Given the potential for significant morbidity and mortality, timely diagnosis is of utmost importance. Diagnosis of HIT should be based on both clinical judgment and laboratory assessment. The patient’s presentation and history provide the most important information for initial determination of likelihood of HIT, but verification of anti-heparin/PF4 antibodies through serum or plasma analysis is a significant step for guiding treatment and follow-up.

4.1 Clinical diagnosis

The Four T’s (4T) score can be used to calculate the pre-test probability of HIT in patients experiencing signs or symptoms of the disorder (Warkentin & Heddle, 2003). The 4T score takes into account four domains and generates a score of 0–8 points depending on the patient’s signs and symptoms; a total score of 0 to 3 indicates that HIT is unlikely; 4 to 5 indicates an intermediate probability; 6 to 8 indicates high likelihood of HIT. In addition to the severity of thrombocytopenia, the score also takes into account the timing of the fall in platelet count, the occurrence of thrombosis or other sequelae, and the presence of other potential causes of the thrombocytopenia. In general, studies have found that the 4T score has high sensitivity for diagnosis (>95%), but specificity is low, especially in ICU patients (Lo et al., 2006; Pouplard et al., 2007). Most authors suggest that those patients with a high likelihood of HIT based on 4T score should be immediately withdrawn from heparin therapy, be treated with an alternative, and be monitored closely while laboratory tests for HIT antibodies are performed. Withdrawal of heparin should not wait until laboratory results are obtained in any patient where HIT is being strongly considered.

Several other sets of criteria and scoring systems have been developed for determining pre-test probability of HIT in both general and specific populations (e.g. Messmore et al., 2011). The HIT Expert Probability Score has recently been developed based on a panel of expert opinions (Cuker et al., 2010), but data regarding its psychometric properties are still lacking. Scoring systems for patients on hemodialysis (Yamamoto et al., 1996) have been created owing to the unique factors associated with HIT in this population. It has also been noted that the use of some scoring systems, such as the 4T score, should be modified in the setting of a critically ill patient; in such cases more emphasis should be placed on ruling out other causes of thrombocytopenia (Hall et al., 2010).
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Table 1. Non-Chemotherapeutic Agents other than Heparin and Low Molecular Weight Heparin that may cause Thrombocytopenia in the Hospitalized Patient

4.2 Laboratory diagnosis
Both functional and immunologic assay tests are available for the detection of HIT antibodies. Functional tests work by detecting antibodies that induce heparin-dependant platelet activation whereas immunologic tests detect circulating anti-heparin/PF4
antibodies, regardless of their ability to activate platelets. Immunologic assays, such as polytypic ELISA, IgG-specific ELISA, and particle gel immunoassay (PGI) have a sensitivity of over 95%, but the specificity is sub-optimal and true positive diagnosis is identified in as few as half of all cases. Due to the pathogenicity of IgG, assays that are specific to this antibody are more likely to yield a true positive diagnosis than the general ELISA assays. Immunologic tests are relatively rapid, producing results within hours. Because of the high sensitivity and the fast turn-around, they are often used to rule-out HIT, but a positive test needs to be interpreted in conjunction with clinical data (Amiral, 1999; Amiral & Vissac, 1999). Mistakenly diagnosing and treating for HIT based on positive assay in the setting of a low pre-test probability score could result in serious consequences, such as venous limb gangrene or fatal hemorrhage (Smythe et al., 2011).

Functional assay tests, such as serotonin release assay (SRA), flow cytometric detection and heparin-induced platelet aggregation (HIPA) assay, have a slightly lower sensitivity (approximately 90%), but a much better specificity (>90%) than the immunologic assays. Therefore, the overall accuracy of the test for correctly identifying HIT is high (Warkentin, 2002). However, these tests are technically more demanding and are only offered at a minority of laboratories. Therefore, they are not relevant in most clinical settings.

The HemosIL AcuStar HIT-IgG (specific for IgG anti-PF4/heparin antibodies) and the HemosIL AcuStar HIT-Ab (for detecting IgG, IgA and IgM anti-PF4/heparin antibodies) are newer laboratory tests available for diagnosing HIT. These two semi-quantitative chemiluminescent immunoassays provide results in 30 minutes and can be run for single sample testing. Legnani and colleagues (2010) reported on initial data showing a 100% sensitivity and negative predictive value for these tests, making them ideal for ruling out HIT. Specificity for the HIT-IgG test was 96.5% and for the HIT-Ab test was 81.2%. These tests, especially the IgG specific test, may gain more use in the future depending on results of further studies.

A recent article advocates the use of a colorimetric test to detect HIT (Prechel et al., 2011). The test uses a tetrazolium-based indicator dye that reacts to the activity of platelets. When contact is made with inactivated or mildly activated platelets, the dye metabolizes to a dark color. When the platelets are highly activated (e.g. due to the presence of HIT antibodies) the dye is unable to metabolize and remains light in color. Preliminary analyses have shown this platelet activation assay test to have between 96% and 100% agreement with the functional assay C-SRA for HIT diagnosis. In general, pairing the findings of a clinical diagnostic score with the results of a laboratory test significantly increases the sensitivity and specificity of the diagnostic yield (Demma et al., 2011; Ruf et al., 2011; Kim et al., 2011).

5. Treatment

When HIT is suspected or proven, all heparin and LMWH should be discontinued. A careful investigation for heparin exposure from sources such as catheter flushes and hemodialysis is necessary. Even the low doses used to flush a catheter can lead to worsening thrombocytopenia and a systemic reaction in patients with HIT, as in the case presented above. Once heparin therapy is discontinued, platelet count should begin to rise within three days, though this is dependent on the amount of antibodies present in the system (Seleng et al., 2007; Kelton, 2002).
There are several important principles in the management of HIT. The American College of Chest Physicians published evidenced-based clinical practice guidelines for the treatment and prevention of HIT in 2008 (Warkentin et al., 2008). Given the prothrombotic nature of the disorder, alternate, non-heparin anticoagulants should be administered. Just discontinuing UFH or LMWH or substituting warfarin (Coumadin®) is associated with a significant risk of thrombosis (Warkentin et al., 1998). As test results may take days to come back, treatment cannot wait until final confirmation of the diagnosis is made and should be instituted if the diagnosis is highly suspected.

For patients who develop a thrombotic event while on heparin or soon after discontinuing heparin, the platelet count should be checked and alternate non-heparin anticoagulants should be used until HIT is excluded.

Low molecular weight heparins, such as enoxaparin (Lovenox®) and dalteparin (Fragmin®) cannot be used in patients who develop HIT due to UFH as there may be cross-reactivity. The use of vitamin K antagonists such as warfarin is contraindicated during the acute phase of the illness when the patient is thrombocytopenic to avoid complications such as venous limb gangrene (Srinivasin, 2004; Warkentin et al., 1997) and multicentric skin necrosis (Warkentin et al., 1999). If the patient is on warfarin at the time HIT is diagnosed, Vitamin K should be administered. Platelet transfusions should generally be avoided, although there have been reports of their use without complication (Hopkins & Goldfinger, 2008; Refaai et al., 2010). IVC filters are not recommended during acute HIT (Warkentin et al., 2008). Ultrasound of the lower extremity can be considered as presence of DVT will affect the duration of anticoagulation (Tardy et al., 1999).

Choice of alternative, nonheparin anticoagulants include direct thrombin inhibitors (DTIs), such as argatroban and lepirudin (Refludan®, the heparinoid danaparoid (Orgaran®), and possibly the Xa inhibitor, fondaparinux (Arixtra®). Argatroban and lepirudin are approved for treatment of HIT in the United States. Danaparoid has not been available in the United States since 2002. Choice of agent depends on a number of factors including availability and the presence of renal or hepatic dysfunction. An important difference between the DTIs is that argatroban is primarily hepatically eliminated, while lepirudin is primarily renally eliminated. The dose of argatroban should be reduced in the setting of liver dysfunction, congestive heart failure, anasarca, and after cardiac surgery. Lepirudin needs be adjusted for patients with renal insufficiency. Adjustments in the doses of these medications should be based on the aPTT. DTIs can elevate the INR and this can complicate the transition to warfarin when the thrombocytopenia has resolved.

Other DTI's have been utilized for the treatment of HIT. Bivalrudin is approved for patients with HIT or at risk for HIT undergoing percutaneous coronary intervention. This agent undergoes enzymatic proteolysis and a minority is excreted renally. Desirudin, another DTI, showed promise as a more economical alternative to argatroban in a recent, small pilot study (Boyce et al., 2011). In addition, observational studies examining the role of desirudin in HIT in patients undergoing orthopedic and cardiac surgery have shown some positive results (Duncan et al., 2011; Levy & Koster, 2011). Desirudin is given subcutaneously every 12 hours as opposed to the other DTI’s mentioned above, which are given as continuous intravenous infusions. Factor Xa inhibitors make an attractive option for use in HIT. Fondaparinux can be given once a day subcutaneously. It costs less and requires less monitoring than the DTIs (monitoring of coagulation parameters to adjust dosing is not required). However, large randomized trials are lacking and it is not approved by the FDA for use in HIT. It has been
used to successfully treat HIT (Lobo et al., 2008), though there have been case reports of worsening thrombocytopenia in patients with HIT or a history of HIT treated with fondaparinux (Pistulli et al., 2011; Warkentin et al., 2007; Modi et al., 2009; Rota et al., 2008). Newer Xa inhibitors such as Rivaroxiban that can be taken orally are becoming available, however their role in the treatment of HIT is not yet known. For patients requiring longer term anticoagulation once the HIT has resolved, a transition to warfarin can be made. It should not be done until the platelet count has improved to at least 150K/uL and there should be an overlap of at least 5 days of warfarin and the non-heparin anticoagulant (Warkentin et al., 2008).

For patients who require anticoagulation with heparin and have a remote history of HIT, heparin can be used for a short duration when antibody assays are negative. Anti-heparin/PF4 antibodies are usually undetected by 100 days after discontinuation of heparin therapy (Warkentin & Kelton, 2001b). For those who are antibody positive, or those who need prolonged anticoagulation, a non-heparin alternative should be considered (Warkentin et al., 2008).

6. Conclusion

HIT is an important clinical entity to recognize as it creates a prothrombotic state that can lead to a variety of thromboembolic and systemic consequences. These most commonly include DVT and PE, though arterial thrombosis, acute myocardial infarction, stroke, acute adrenal insufficiency, and other serious complications can occur. Patients with HIT given an IV bolus of heparin may experience acute systemic reactions that can simulate pulmonary embolus or sepsis and even lead to cardiac arrest. Treatment includes discontinuation of all UFH and LMWH. A thorough search for surreptitious sources of heparin exposure should be performed. An alternative, non-heparin anticoagulant, such as a DTI should be started. HIT should be considered in patients who develop DVT or PE who are either receiving or have recently discontinued heparin. Intravenous heparin or LMWH should not be utilized to treat thrombosis in these situations. In the future, newer DTI’s and possibly factor Xa inhibitors may simplify treatment and reduce cost in managing this condition.

7. References

thrombocytopenia provoke direct activation of microvascular endothelial cells. *International Immunology*, vol.14, no.2, (February 2002), pp.121-129.


According to Virchow’s triad, venous thrombosis can occur as a result of one or more of three factors: changes in the dynamics of the blood flow, endothelial injury/dysfunction of the blood vessel and hypercoagulability. The blood in the veins is constantly forming microscopic thrombi that are routinely broken down by the body, and significant clotting can occur only when the balance of thrombus formation and resolution is altered. This book is a fresh synthesis of venous thromboembolism care and considers the opinions and studies from different fields of medicine. As venous thrombosis spectrum is wide and can affect many organ systems, from deep veins of the leg to the cerebral venous system, our intent is for this to be a comprehensive, up-to-date and readable book. We tried to present a synthesis of existing material infused with new ideas and perspectives and authors own clinical studies and even case-reports.

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