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Venous Thromboembolism in Neonates, Children and Patients with Chronic Renal Disease – Special Considerations

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1. Introduction

1.1 Venous thromboembolism in neonates

Among children, the group of critically ill newborns presents the largest of population that suffering from thromboembolism. Making decisions regarding therapeutic strategies a challenge for the intensive care physician as the clinical significance of neonatal thrombosis varies from asymptomatic incidents to life or limb threatening events and, moreover, appropriate evidence-based treatment algorithms are lacking.

This review focuses on the incidence, pathophysiology, risks factors, diagnosis and treatment of venous thromboembolism in neonates

1.2 Incidence

The incidence of thromboembolic events in the pediatric age group is highest in neonates and infants <1 year of age (Monagle et al., 2008). Much of the published data regarding the epidemiology of neonatal venous thromboembolism (VTE) has come from national registry studies. The Canadian registry (Schmid & Andrew, 1995) reported 97 cases of which 64 (66%) had venous involvement. The German neonatal registry (Nowak-Gottl et al., 1997) reported 79 cases of symptomatic thrombosis, including stroke. VTE accounted for 76% of cases. The overall incidence of symptomatic events was 0.51 per 10,000 births.

Male and female infants are affected with equal frequency with the exception of renal vein thrombosis, which has a male predominance for unclear reasons (Chalmers, 2006).

1.3 Pathophysiologic

We must consider the multiple additive factors that contribute to the development of thromboembolism in neonates. Also, the hemostatic system of neonates is significantly different from that of children and adults (Veldman, 2008).

On the pro-coagulant side, especially the vitamin K-dependent coagulation factors (II, VII, IX, and X) and the components of the contact system (FIX,FXII, prekallkreine and high molecular weight kininogen) show significantly reduced plasma activities in neonates compared to children and adults. However, the vitamin K-dependent inhibitors of coagulation, protein C and protein S, are also reduced, counterbalancing the reduced clotting potential of neonatal plasma. In fact, both antithrombin and protein C concentrations are decreased to approximately 30% of adults values in term and even lower in preterm newborns. Neonatal platelets have been reported to be hypo-reactive; however, this deficiency seems to be balanced by increased von Willebrand factor activity, resulting in overall normal platelet function (Veldman, 2008).

The activity of the fibrinolytic system in the newborn is reduced compared to adults and older children due to both decreased plasma activity of plasminogen and increased plasma levels of plasminogen activator inhibitor (PAI). The latter fact may explain the high rate of thromboembolic event (TE) associated with intravascular devices in newborns. However, to date there is no evidence that the neonatal hemostatic system either protects from or promotes thrombus formation. Of course, additional risk factors, eg, critical illness or congenital thrombophilia, have to be considered separately from the immaturity of neonatal hemostasis (Veldman, 2008). Given the significant differences between the plasma factor concentrations in different age groups, a detailed knowledge on the development of hemostasis is critical for the intensivist in order to adapt pharmacological approaches and interpret results from laboratory tests in the neonate with TE (Ignjatovich et al., 2006; Ignjatovich et al., 2007).

1.4 Risk factors

Neonatal VTE is frequently associated with presence of significant underlying risk factors. As in older children central venous lines (CVLs) are the single most important contributing factor. Excluding cases of renal vein thrombosis (RVT), CVLs-related thrombosis accounted for 89% and 94% of VTE in the Canadian and Dutch registries, respectively (Schmidt and Andrew, 1995; van Ommen et al., 2001). These events involve the large vessels most frequently used for catheterization including the umbilical vein. Neonatal VTE related to the use of the umbilical venous catheter (UVC) has been the subject of studies involving sequential imaging. Using venography, Roy et al.,1997 documented UVC-associated thrombosis in 14 of 48 neonates (29%). As in older children, many of these events were asymptomatic and the incidence of thrombosis was highly dependent on the imaging modality used (Chalmers, 2006).

Critical illness is a well-recognized risk factor for TE in all age groups. Immobilization, rapid changes in intravascular volume and extensive intravascular instrumentation contribute to the enhanced risk of venous and arterial thrombosis in patients in intensive care units. (Veldman, 2008). Additional risk factors include, but are not limited to, asphyxia, maternal diabetes, poor cardiac output and dehydration. Neonates are born with a high hematocrit and tend to contract their intravascular volume within the first days of life, making them even more prone to thromboembolic events (Veldman, 2008).

In the neonatal population, sepsis is particularly devastating, as it causes 45% of late deaths in the neonatal intensive care unit (NICU). Neonates with sepsis develop an acquired pro-thrombotic state due to increased consumption of already limited supplies of coagulation

inhibitors. Furthermore, plasma activity of plasminogen activator inhibitor (PAI) is increased in sepsis and levels of protein C are reduced. The latter fact has been reported to correlate with poor outcomes in adults and neonates. Ongoing consumption of coagulation factors and platelets resulting in microcirculatory thrombosis likely contributes to sepsis-induced multi-organ failure and death. Macro-circulatory thrombotic events are rare in this setting but can occur, especially in babies who have arterial umbilical catheters (UACs) or UVCs in situ (Veldman, 2008).

Turebylu., 2007 reported that congenital thrombophilia not to be associated with UVC thrombosis. Revel-Vilk et al., 2003 reported that in neonates inherited prothrombotic coagulation proteins do not contribute significantly to the pathogenesis of venous TEs; they concluded that the most significant aetiological risk factors are the presence of a central venous line and other medical conditions.

Heller et al., 2000 reported an elevated odds ratio for the presence of congenital thrombophilia in neonates with renal, portal or hepatic venous thrombosis and recommended that neonates with TE should undergo an extensive screening, included resistance to activated protein C (APC-R), protein C, protein S, antithrombin activity, activities of coagulation factors VIIIc and XII, lipoprotein-A, histidine-rich glycoprotein, heparin cofactor II, antiphospholipid antibodies, lupus anticoagulants, as well as fasting homocysteine concentrations. In addition, DNA-based assays (factor V G1691A mutation or factor V Leiden, factor II G20210A variant and MTHFR C677T genotype) should be considered. Whereas DNA-based mutation analysis can be performed at any time point, protein-based assays should not be carried out in the first 6-8 months after the event and oral anticoagulation is recommended to be discontinued at 14-30 days before plasma samples for thrombophilia diagnosis are drawn.

Deficiency of one of the important hemostasis control proteins, protein C, protein S or antithrombin, occurs less frequently, but results in a more potent prothrombotic state. Heterozygous deficiency of these proteins is difficult to diagnose in the newborn period, because the neonatal levels are much lower than the adult reference range. Homozygous deficiency of Protein C or S typically presents in the perinatal period with significant thrombosis resulting in purpura fulminans. Compound heterozygosity of one of the natural anticoagulants in association with Factor V Leiden may cause a similar clinical picture (Beardsley, 2007).

1.5 Diagnosis

1.5.1 Clinical

Intravascular catheters are responsible for more than 80% of venous thrombotic complications. Signs and symptoms of catheter-related thrombosis vary from diminished blood flow through the catheter to tenderness and swelling of the affected extremity or swelling of the neck and head associated with superior vena cava syndrome. Although clinically apparent thrombi occur in less than 5% of neonates with a central line. (Beardsley, 2007).

Renal vein thrombosis (RVT) is the most common form of non-catheter-related thrombosis (Nathan et al., 2003). Risk factors for RVT include maternal diabetes, dehydration, infection, asphyxia, polycythemia, prematurity, critical illness, femoral CVL and male gender (chest, 913, veldman). Approximately 80% present within the first month and usually within

the first week of life and it is likely that a number of these events initially develop antenatally. (Monagle et al., 2008; Veldman, 2008). Presenting symptoms and clinical findings are different in neonates and older patients and are influenced by the extent and rapidity of thrombus formation. Neonates usually have a flank mass, hematuria, proteinuria, thrombocytopenia and nonfunction of the involved kidney. (Nathan et al., 2003). Approximately 25% of cases are bilateral and 52-60% are reported to have evidence of extension into the inferior vena caval (IVC). (Monagle et al., 2008). Overall survival following neonatal RVT is generally favorable. Four small cohort studies with variable follow-up reported 81-100% of neonates survived. Clinical sequelae included chronic renal impairment and hypertension. (Monagle et al., 2008)

Thrombosis of the inferior vena cava can present with signs resembling obstruction of the renal vein (hematuria and retroperitoneal mass); however, these will occur bilaterally when the inferior vena cava is affected. In addition, the lower limbs may be edematous and, if blood flow is substantially impaired, the child may be in respiratory distress and may have high blood pressure. (Veldman, 2008)

Signs of impaired liver function, hepatomegaly and splenomegaly should raise the suspicion of portal vein thrombosis (PVT); however, only about 10% of children with PVT develop acute clinical symptoms (Veldman, 2008).

1.5.2 Imaging

The echocardiography or abdominal ultrasound is the most commonly applied diagnostic method to confirm clinical suspicion of TE or to screen babies for clinically silent disease. (Roy et al, 2002) comparing echocardiographic investigations with venograms and reported a sensitivity of 21-43% and specificities ranging from 76-94%. This study concluded that venography is required to accurately diagnose UVC related TE in neonates.

1.5.3 Laboratory

Initial laboratory work-up in a neonate in whom thrombosis is suspected should include a full blood count as well as a coagulation screening with determination of prothrombin time, thrombin time and activated partial thromboplastin time.

D-dimers are a positive finding in almost all critically ill neonates. Conversely, negative D-dimers are relatively accurate in ruling out thrombosis in most patients, including neonates.

In almost all neonates, platelet numbers decrease after birth. However, a sudden and severe drop in platelet counts should alert the intensivist. The thrombocytopenia remains one of the most sensitive indicators for micro- (in the setting of sepsis) or macro-circulatory thrombosis (Veldman, 2008).

Also it has been recommended that infants who are diagnosed with clinically significant VTE should undergo testing for inherited and acquired thrombophilic traits. (Beardsley, 2007).

1.6 Management

There are no published randomized controlled trials (RCTs) and no large cohort studies that report on the outcomes of different treatment modalities in the management of neonatal

VTE. Valuable and comprehensive evidence-based clinical practice guidelines have been developed by the American College of Chest Physicians (ACCP) on antithrombotic therapy in neonates and children (Monagle et al, 2008). Their recommendations are necessarily based on extrapolation of principles of therapy from adult guidelines, limited clinical information from registries, individual case studies and knowledge of current common clinical practice.

The following is the summary of the recommendations of the ACCP 2008 on Anticoagulation and Thrombolytic Therapy for neonates with VTE: We suggest that central venous lines (CVL) or UVCs associated with confirmed thrombosis be removed, if possible, after 3 to 5 days of anticoagulation (Grade 2C). It is a weak recommendation. We suggest either initial anticoagulation, or supportive care with radiologic monitoring (Grade 2C); however, we recommend subsequent anticoagulation if extension of the thrombosis occurs during supportive care (Grade 1B). It is a strong recommendation. We suggest anticoagulation should be with either of the following: (1) LMWH given bid and adjusted to achieve an anti-FXa level of 0.5–1.0 U/mL; or (2) UFH for 3 to 5 days adjusted to achieve an anti-FXa of 0.35 to 0.7 U/mL or a corresponding APTT range, followed by LMWH. We suggest a total duration of anticoagulation of between 6 weeks and 3 months (Grade 2C). We suggest that if either a CVL or a UVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH be given to prevent recurrent VTE until such time as the CVL or UVC is removed (Grade 2C). We recommend against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 1B). We suggest that if thrombolysis is required the clinician use tPA and supplement with plasminogen fresh frozen plasma) prior to commencing therapy (Grade 2C). For neonates or children with unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava, we suggest supportive care with monitoring of the RVT for extension or anticoagulation with UFH/LMWH or LMWH in therapeutic doses; we suggest continuation for 3 months (Grade 2C). For unilateral RVT that extends into the inferior vena cava, we suggest anticoagulation with UFH/LMWH or LMWH for 3 months (Grade 2C). For bilateral RVT with various degrees of renal failure, we suggest anticoagulation with UFH and initial thrombolytic therapy with TPA, followed by anticoagulation with UFH/LMWH (Grade 2C). Remark: LMWH therapy requires careful monitoring in the presence of significant renal impairment.

2. Venous thromboembolism and chronic kidney disease

Pulmonary embolism and Deep Vein Thrombosis are a wide spectrum of a single disease defined as Venous Thromboembolism, and it occurs for the first time in approximately 100 persons per 100,000 each year in the United States and rises exponentially from less than 5 cases per 100,000 persons at 15 years and less to approximately 500 cases per 100,000 persons at age 80 years (White, 2003; Ageno, 2006; Heit, 2008).

An understanding of the risk factors for venous thrombosis is necessary in order to increase the prevention of this disease in high risk individuals and groups of patients.

The major risk factors for thrombosis include endogenous pattern characteristics like obesity and genetic factors, and triggering factors such as surgery, immobility or pregnancy. Venous thrombosis tends to occur due to additive effects of endogenous, genetic and environmental risk factors present simultaneously (Cushman, 2007).

Chronic kidney disease is common in the general population, affecting 13% of adults in the United States between 1999 and 2004 (Coresh 2007).

There are several questions about the relation between venous thromboembolism and chronic kidney disease. Is the chronic kidney disease a risk factor for venous thromboembolism? What are the mechanisms involved in these diseases? And finally how to treat these patients?

2.1 Epidemiology of thromboembolism associated to chronic kidney disease

2.1.1 Chronic kidney disease and venous thromboembolism

There are few prospective studies about this association, with this objective and using the data from the Longitudinal Investigation of Thromboembolism Etiology Study, 19,073 middle-aged and elderly adults were categorized on the basis of the determination of the glomerular filtration rate and cystatin C (data available in 4,734 participants). During a mean follow up time of 11.8 years, 413 participants developed venous thromboembolism (41% idiopathic and 59% secondary). Compared with the participants with normal kidney function, the relative risk for venous thromboembolism was 1.28 (95% confidence interval) for those with mildly decrease kidney function and 2.09 for those with stage 3 or 4 of chronic kidney disease. The authors concluded that middle-age and elderly patients with chronic kidney disease stages 3 through 4 evidence all increased risk for incident venous thromboembolism, suggesting that prophylaxis may be particularly important in this population (Wattanakit, 2008).

Similar results were reported by Folsom et al, in a prospective cohort of 10,700 patients, in whom estimated the glomerular filtration rate from prediction equations based on serum creatinine or cystatin C, and follow up for the occurrence of venous thromboembolism for over a median of 8.3 years. The adjusted hazard ratios of total venous thromboembolism and estimated glomerular filtration rate based in cystatin C was 1.0 for normal kidney function, 1.4 for mildly impaired renal function and 1.94 for stage 3 and 4 of chronic kidney disease, these hazard ratios were moderately attenuated to 1.0, 1.26 and 1.6 respectively with adjustment for hormone replacement therapy, diabetes and body mass index. Association between chronic kidney disease, based on estimated glomerular filtration rate using cystatin C, and venous thromboembolism were slightly stronger for idiopathic venous thromboembolism than for secondary venous thromboembolism. In contrast, creatinine glomerular filtration rate was no associate with total venous thromboembolism occurrence.(Foslom, 2010).

Another prospective cohort study 8,495 subjects whit chronic kidney disease stages 1 to 3 in which renal function and albuminuria were assessed, they concluded that stages 1 or 2 of chronic kidney disease are risk factors for venous thromboembolism in presence of albuminuria, and the risk of venous thromboembolism is more related to albuminuria than to impaired glomerular filtration rate (Ocak 2010).

2.1.2 End-stage renal disease and venous thromboembolism

Independent of co-morbidity chronic dialysis patients have high risk for pulmonary embolism, in 1996 in the United States, the overall incidence rate of pulmonary embolism

was 149.9/100,000 dialysis patients, compared with 24.6/100,000 persons in the general population. In this study the younger dialysis patients had the greatest relative risk for pulmonary embolism (Tveit, 2002). Similar results by Allen et al, that showed an incidence of 8.3% of venous thromboembolism in dialysis patients (Allen, 1987).

2.1.3 Nephrotic syndrome and venous thromboembolism

Several studies consider Nephrotic Syndrome as a risk factor for venous thromboembolism. In one of the largest studies, Kayali et al, studied 925,000 patients discharged from hospitals in the United States with the diagnosis of nephrotic syndrome, 0.5% had pulmonary embolism, 6.5% had deep vein thrombosis and less than 0.5% had renal vein thrombosis. The relative risk of pulmonary embolism (in patients with the nephrotic syndrome) was 1.39 and for deep vein thrombosis was 1.72. Among patients aged 18-39 years the relative risk of deep vein thrombosis increases to 6.81 (Kayali, 2008).

Another prospective study of 298 patients with nephrotic syndrome, with a mean follow up of 10±9 years, the annual incidence of venous thromboembolism was 1.02%, over the first 6 months of follow up; the rate of venous thromboembolism was 9.85. In this group of patients, proteinuria and serum albumin levels tended to be related to venous thromboembolism, however, only the predictive value of the ratio of proteinuria to serum albumin was significant but not the estimated glomerular filtration rate. (Bakhtawar, 2008)

For instance, estimated glomerular filtration rate using cystatin C, albuminuria and ratio proteinuria to serum albumin have predictive value for venous thromboembolism in patients with chronic renal disease.

2.1.4 Renal transplantation and venous thromboembolism

In renal transplantation, few studies had evaluated the risk of venous thromboembolism, the largest one used the United States Renal Data System database to study 28,924 patients receiving a kidney transplant, the rate of VTE occurring 1.5 to 3 years after transplantation was 2.9 episodes/1,000 person-years. Estimated glomerular filtration rate less than 30 mL/min/1.73 m² versus higher at the end of the first year after renal transplantation was associated with significantly increased risk for later venous thromboembolism (adjusted hazard ratio, 2.05; 95% confidence interval, 1.08 to 3.89). Patients with severe chronic kidney disease, after renal transplantation should be regarded as high risk for late venous thromboembolism, which is a potentially preventable cause of death in this population (Abbott, 2004).

A prospective study of a cohort of 578 patients with renal transplantation, reports 9.1 % incidence of deep vein thrombosis of the lower limbs, 39.5% were asymptomatic and the diagnosis was made during routine ultrasound examination. Those patients, who experience venous thromboembolism, were at high risk of recurrence after thromboprophylaxis withdrawal (Poli, 2006).

Co-morbidities like diabetes mellitus could increase the risk of venous thromboembolism, in a prospective study the frequency of deep vein thrombosis during the first 3 weeks after kidney transplantation has been evaluated using the combination of thermography and strain-gauge plethysmography for objective diagnosis. 83 consecutive

patients were included, 33 with juvenile diabetes mellitus. The overall frequency of thrombosis was 24.1%, diabetes mellitus being a significant risk factor (Bergqvist, 1985).

Epidemiological studies have attempted to define risk in terms of modifiable (drugs, dialysis modality, surgical procedure) and non-modifiable (age, diabetes mellitus, vascular anomalies, factor or identify changes in coagulation or fibrinolysis) promoting a more thrombotic state. Most recently the evolution of thrombophilia research has established the potential for inherited hypercoagulability to predispose to acute allograft thrombosis. Inheritance of the factor V Leiden (FVL), prothrombin G20210A mutation, or the presence of antiphospholipid antibodies may increase the risk of renal allograft thrombosis certain 3-fold in selected patients. Patients with end-stage renal disease due to systemic lupus erythematosus appear at particularly high risk of thrombosis, especially if they have either antiphospholipid antibodies or detectable β 2-glycoprotein-1. (Irish, 2004).

2.2 Mechanisms of venous thrombosis in patients with chronic kidney disease

The individual risk of venous thromboembolism varies as a result of a complex interaction between congenital and transient or permanent acquired risk factors.

Virchow summarized the pathophysiology of venous thromboembolism in his famous triad: venous stasis, endothelial damage and hypercoagulability (Ageno 2006 as cited in Virchow, 1856)

Stasis predisposes to venous thrombosis by reducing the clearance of activated coagulation factors, the mixing of this activated coagulation factors and inhibitors and the dilution of activated coagulation factors.

Vessel wall damage is more important in the pathogenesis of arterial thrombus. Venous endothelial damage results in endothelial cell detachment and exposure of blood to tissue factor and other subendothelial components that activate coagulation.

Hypercoagulable states could be in several situations: increase thrombin production following surgery or decrease activity of endogenous anticoagulants.

On the whole, venous thromboembolism probably has been understood as a multicausal disease in which more than one genetic or environmental condition coincides to produce clinically apparent thrombosis (Rosendaal, 1999).

2.2.1 Procoagulant markers

To elucidate the mechanisms that could increase the risk of venous thromboembolism in patients with chronic kidney diseases, some studies had investigated the levels of the procoagulant markers.

Patients with end stage renal disease and predialysis renal failures, nephrotic syndrome and mildly chronic kidney disease had elevated level of C Reactive Protein, fibrinogen, d-dimer, Factor VIII, Factor VII, and Von Willebrand, these high levels are due to increase synthesis out of proportion to urinary loss while lower levels of coagulation factors like IX, XI, and XII due to increased urinary loss (Keller, 2008; Vaziri, 1980). On the other hand, an association between increased levels of coagulation factors VIII, FIX and F XI and an increased risk of venous thromboembolism has been reported, the mechanisms and clinical significance of such association are still unclear (Crowther, 2003).

2.2.2 Decrease endogenous anticoagulants

In the nephrotic syndrome the hypercoagulable state is distinguished by an increase in coagulation factors (V, VIII and fibrinogen) a decrease in the levels of antithrombin III and S Proteins, an increase in alpha 2 antiplasmin activity and exaggerated platelet adhesiveness and aggregation. This prothrombotic state may be aggravated by additional rheological factors (immobilization, diuretic therapy, etc.) (Keusch, 1989; Adams, 2008).

The lower level of antithrombin III in patients with nephrotic syndrome is probably due to increased urinary loss. (Vaziri, 1984).

2.2.3 Platelet activation and aggregation

P-selectin is a marker of platelet activation and is increased in nephrotic syndrome patients. Platelet aggregation increases because of hypoalbuminemia that result in an increase availability of thromboxane a-2 that is a potent platelet agonist (Jackson, 1982).

2.2.4 Reduced fibrinolysis

Fibrin clots with reduced permeability, increased clot stiffness and reduced fibrinolysis susceptibility may predispose to thrombosis. Using permeability and turbidity studies in 22 end stage renal disease patients and 24 healthy controls. Fibrin clots made from plasma of patients with chronic renal disease were found to be less permeable, less compactable and less susceptible to fibrinolysis than clots from controls (Sióland, 2007).

Another study in 33 patients in long term haemodialysis has demonstrated unfavorably altered clot properties that may be associated with increase cardiovascular mortality (Unaas, 2008) There are studies that demonstrates that individuals with reduced fibrinolytic potential as measured by plasma based assays, have an increased risk of developing a first venous thrombosis. Whether this hypofibrinolytic state determined by genetic or acquired factors or a combination of them and which proteins are evolved is at present unknown (Lisman, 2005).

In conclusion, chronic kidney disease patients presents a pro-thrombotic state that increases the risk of venous thromboembolism and comprises alteration of platelet functions, coagulation factors, endogenous anticoagulants and fibrinolytic system, many mechanism are still unknown and opens a potential field for investigation.

2.3 Treatment of venous thromboembolism in chronic renal disease patients

Anticoagulants are widely used to prevent and treat venous thromboembolism, these drugs are often used in patients with renal impairment. Renal impairment is at the same time, a risk factor for bleeding and thrombosis during anticoagulant therapy and may influence the balance between the safety and efficacy of such drugs (Harder, 2011).

The available anticoagulants for the treatment of thromboembolism are heparins, the Factor X inhibitor fondaparinux, warfarin and the new anticoagulants Factor X inhibitors and direct thrombin inhibitors. Most of the antithrombotics are eliminated primarily by the kidneys, so dosing in patients with several renal impairment may require dosage reduction or increase frequency of monitoring for bleeding and thromboembolism complications or both (Lobo, 2007).

Decisions for anticoagulation therapy respect the agent selected, dose, duration of treatment, and approaches to monitoring should balance the risks between bleeding and thrombosis.

2.3.1 Indirect thrombin Inhibitors

2.3.1.1 Unfractionated Heparin (UFH)

Heparin is a large, heterogeneous compound of approximately 45 saccharide units that indirectly binds to and increases the enzymatic activity of antithrombin III, against activated Factors II, and X. Unfractionated Heparin clearance is the result of a combination of rapid, saturable mechanism via the endothelium and the reticuloendothelial system in liver, and a slower, non saturable mechanism through the kidneys (Follea, 1987) However UFH remain the anticoagulant choice for in-hospital treatment of patients with thromboembolic disorders who also have renal dysfunction.

There are no recommendations from the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy and from the manufacturers for dose reduction of UFH in patients with chronic renal impairment (Kearon, 2008). The monitoring of the activated partial thromboplastin time is recommended while UFH are administered to renal impairment patients.

In acute thromboembolic events, an intravenous bolus dose up to 80 units/kg may be administered, but in the absence of an emergent need for anticoagulation or high risk situations, the bolus dose could be omitted and just a continuous infusion may be initiated with the advantage of gradually establishing of the anticoagulation and limiting the risk of bleeding. Initial continuous infusion of unfractionated heparin do not require special adjustments because of chronic kidney disease alone and goal activated partial time of thromboplastin should be targeted to the indication for anticoagulant therapy. Another option is subcutaneous weight adjusted dosing. (Dager, 2010)

2.3.1.2 Low molecular weight heparin (LMWH)

Low molecular weight heparins may not be considered as the preferred option for initial parenteral anticoagulation in chronic kidney disease patients, but they could be considered in special situations because these agents are primarily eliminated on kidneys and dosing adjustments are needed as renal failure progresses (Kearon, 2006).

A meta analysis was performed to study the incidence of bleeding in chronic kidney disease patients treated with low molecular weight heparins like enoxaparin, dalteparin and tinzaparin. Enoxaparin has elevated levels of anti-factor Xa and an increased risk for mayor bleeding, suggesting empirical dose adjustment of enoxaparin in patients with severe renal impairment. In patients with mild to moderate renal impairment there are not required dose adjustment of enoxaparin [Lim, 2006]

For venous tromboembolism prophylactic doses of enoxaparin the American College of Chest Physicians (ACCP) recommendations for patients with severe renal impairment is to lower or halve the standard dose. For the treatment of venous thromboembolism in patients with severe renal impairment the ACCP guidelines recommended either using unfractionated heparin instead of low molecular weight heparins. No specific dose recommendations are made in this guidelines for other low molecular weight heparins in

venous thromboembolism. For tinzaparin and dalteparin monitoring of anticoagulant activity in patients with renal failure should be considered.

2.3.1.3 Fondaparinux

Fondaparinux is a synthetic pentasaccharide, that inhibits factor Xa by binding to antithrombin. After subcutaneous administration the peak plasma concentration is achieved within 2 hours, the half life is 17 hours in young healthy subjects and 21 hours in the elderly. Up to 80% of fondaparinux is eliminated as unchanged drug via the kidneys.

However the ACCP guidelines for VTE prevention do not recommend specific doses adjustments for fondaparinux in renal impaired patients, depending of the circumstances the guidelines recommended avoiding the anticoagulant, lowering dose or monitoring anticoagulant activity [Hirsh,2008]

The summary of manufacturers insert states contraindicated of fondaparinux in patients with severe renal impairment (clearance of creatinine <20 ml/min) and use with caution in patients with moderate renal impairment (creatinine clearance 30 a 50 ml/min)[Harder 2011]

2.3.2 Vitamin K antagonists

Vitamin K antagonist inhibit the hepatic synthesis of factors II, VII, IX and X and protein C and S. There are various vitamins K antagonists, however, warfarin is the most commonly used around the world.

After oral administration warfarin is rapidly absorbed reaching the plasma peak concentration within 90 minutes, the peak therapeutic effect is acquired at 36 hours. Warfarin undergoes oxidative metabolism via the CYP450 system in the liver and less than 1% of the drug is excreted unchanged in the urine. (Ansell, 2008)

The risk of bleeding and thromboembolic complications is increased when using warfarin in the chronic kidney disease population and depends of the INR target, incidence of values outside of the target or other comorbid conditions. Warfarin dosing requirements tend to be lower as renal function declines. (Limdi , 2009) Concurrent drug interactions and acute medical problems such as heart failure or infections can influence the dose response to warfarin. Because the complexity of managing warfarin and increased risk of adverse outcomes in the chronic kidney disease setting, warfarin management in those patients should be referred when possible to dedicated anticoagulant services.(Dager ,2003).

2.3.3 Novel oral anticoagulants in patients with renal disease

2.3.3.1 Dabigatran etexilate

Dabigatran etexilate is a direct thrombin inhibitor, currently approved for the prevention of venous thromboembolism in orthopedic surgery patients. After oral administration peak plasma concentrations are achieved within 2 hours of administration. Elimination of dabigatran is predominantly via the renal pathway, 80% of the administered dose is excreted unchanged in the urine within the first 24 hours after an intravenous dose and is contraindicated in patients with severe renal impairment (Stangier, 2008)

Limited data are available on dabigatran pharmacokinetics in patients with renal impairment for venous thromboembolism treatment.(Dahl, 2009)

2.3.3.2 Rivaroxaban

Rivaroxaban inhibits both free and clot-bound Factor Xa, this oral anticoagulant has been approved for the prevention of venous thromboembolism after elective hip or knee replacement surgery in adults (Bauer, 2008)

Rivaroxaban has a dual mode of elimination hepatic and renal and the inhibition of factor Xa activity also increased with the reduce renal function. Rivaroxaban is not recommended for patients with a Creatine clearance of less than 15 ml/min. (Kubitza, 2010). To the date there are not reported studies for rivaroxaban in patients with renal impairment for venous thromboembolism.

2.3.3.3 Apixaban

Apixaban inhibits both free and clot-bound factor Xa Apixaban is rapidly absorbed in the stomach and small intestine, reaching peak concentrations approximately 1 to 3 hours after oral administration. The elimination includes renal and biliary excretion, and the drug has a mean elimination half life of 8 to 15 hours. (Shantsila, 2008; Frost, 2007)

There are limited data about the clearance of apixaban in patients with renal impairment.

In presence of heparin induced thrombocytopenia or antithrombin deficiency direct thrombin inhibitors may be options for anticoagulation. They are argatroban, bivalirudin and lepirudin, available only by continuous venous infusion or subcutaneous injection.

2.3.3.4 Argatroban

Argatroban is eliminated in liver and no adjustment in dosing is required for renal insufficiency or hemodialysis, the mean dose in heparin induced thrombocytopenia was 1.6 µg/kg/min, targeting activated partial thromboplastin time 1.5 to 3.0 times control. In patients with renal failure it has been suggested lower dosing requirements with dose reduction of approximately 0.1 to 0.6 µg/kg/min for each 30 ml/min decrease in the creatinine clearance. (Hursting, 2008; Arpino, 2004)

2.3.3.5 Lepirudin

Lepirudin is the agent most dependent of renal elimination and requires significant dose reductions as renal function declines.

2.3.3.6 Bivalirudin

Bivalirudin is eliminated independent of renal function, with 80% removed enzymatically, it has also been observed to be removed by ultrafiltration. For patients with renal dysfunction and heparin induced thrombocytopenia, dose reductions has been suggested. The extent depends on the degree of renal dysfunction and form of renal replacement therapy. The target activated partial thromboplastin time for both lepirudin and bivalirudin is 1.5 to 2.5 times baseline and argatroban 1.5 to 3 times baseline, which may be different from the range specified for unfractionated heparin. (Dager, 2007; Kiser, 2008).

In conclusion the unfractionated heparin continues been the anticoagulant of choice for chronic kidney disease patients, because it's short half life, reliable monitoring, reversibility and independence of renal function. Of the oral anticoagulants, warfarine is a safe alternative to unfractionated heparin, easy to monitor and does not requires dose alteration in chronic kidney disease.

Stage	Kidney damage	Glomerular filtration rate CrCl, mL/min/1.73m ²
1	Normal or Increased GFR	≥90
2	Mild decrease in GFR	60 to 80
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure (End stage renal disease)	<15(or dialysis)

CrCl: creatinine clearance

^a Classification by National Kidney Foundation. Chronic kidney disease is defined as either kidney damage or GFR of <60 mL/min/1.73m² for ≥ 3 months. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies. GFR reported by the National Kidney Foundation, using the modification of Diet in Renal Disease Study equation based on age, gender, race, and serum creatinine

[Reference: Harder, 2011]

Table 1. Classification of Renal impairment

Anticoagulant	Elimination	Half life*	Monitoring	Antidote	Dose adjustment in severe renal impairment
UFH	RES,renal minimal	30-150 min after IV administration	aPTT, anti Xa ACT	Protamine	No dose adjustment Monitoring high doses
LMWH	Mainly renal RES minimal	2-8 h after SC administration	Anti Xa	Protamine partially effective	Yes
Bivalirudin	Proteolytic cleavage 80% Renal 20%	~25 min after IV administration	ACT	None	Yes
Argatroban	Hepatic 100%(CYP3A4)	40-50 min after IV administration	aPTT,ACT, ECT	None	No
Fondaparinux	Renal>80%	17 -21 h after SC administration	Anti Xa	None	Drug no recommended
Vitamin K agonists	Hepatic 100% (CYP2C9)	~36-42 h	INR	Vitamin K	Careful dose titration
Rivaroxaban	Renal 50% hepatic 50%	7 -11 h	Anti Xa	None	Not recommended
Dabigatran	Renal 80%	8 -10 h	ECT	None	Not recommended
Apixaban	Renal 50%	8 – 15 h	INR, aPTT, Anti Xa	None	Yes

ACT =Activated clotting time; aPTT=activated partial thromboplastin time; CYP= cytochrome p450
ECT = ecarin clotting time; INR= International normalized ratio; IV =Intravenous; LMWH= low molecular weight heparin; RES= reticuloendothelial system; SC= subcutaneous; UFH= unfractionated heparin.
[Reference: Grand’Maison A, Charest A,Geerts W, 2005 ; Harder S,2011]

Table 2. Anticoagulants characteristics and dose adjustment in severe renal impairment

While low molecular weight heparins, fondaparinux and direct thrombin inhibitors may offer alternatives to unfractionated heparin in patients with chronic kidney disease, more evidence are needed to determine the safe dose and monitoring strategy.

3. Thrombosis in infants and children

Thromboembolism (TE) is still regarded as a rare event in childhood and therefore knowledge of diagnostics, therapy and prophylaxis is limited among general pediatricians. During the past years, however, it is increasingly recognized as having significant impact on mortality, chronic morbidity and the normal development of children, which has led to an enhanced sensitivity toward considering such events in respective patients. Besides the greater awareness, an objective increase in childhood thrombosis is due to the medical progress in the treatment of critically ill patients. This seemingly contradictory observation is easily explained by the increasing use of central catheters and innovative interventional procedures in the treatment of premature infants, neonates and older children who are critically ill, suffering from complex cardiac defects, and from malignant disease, respectively. Therapeutic and prophylactic measures have subsequently become increasingly important, but in addition to the complexity of the clinical background and the heterogeneity in the pattern of acquired and inherited risk factors for TE among patients, the physiological significant differences of the coagulation system between newborns, young children and adolescents and differences in drug metabolism do not allow general recommendations for therapeutic interventions like thrombolysis and prophylactic anticoagulation for the different clinical conditions. This situation is further complicated by a lack of availability of pediatric formulations and pediatric data for new drugs.

The increasing knowledge of exogenous and endogenous thrombophilic risk factors has initiated a number of studies to assess the impact of such factors with respect to their contribution to the thrombophilic state, both individually but also in concert with other factors. In addition to their impact on a first thrombotic event, much of the interest is now focused on their importance for thrombotic relapses. Only such studies will give us an answer to questions concerning the indications for treatment, prophylaxis and its optimal duration. All management recommendations are reflecting the authors' experiences and opinions and are not based on evidence gained by controlled trials as such trials are either completely lacking or still ongoing.

3.1 Epidemiology

The annual incidence of TE in childhood in general is considerably lower than in adults, with a reported frequency of 0.07 to 0.14 per 10,000 children or 5.3 per 10,000 referrals of children to the hospital. The results of a prospective German study suggested an incidence of 5.2 per 100,000 neonates, and a prospective Dutch study resulted in an estimate of 1.4 per 100,000 children and adolescents (Parasuraman & Goldhaber, 2006). More than 80% of TE in childhood were on a background of a severe preceding illness or other comparable predisposing factors. (Kuhle et al, 2004) Arterial TE in children is less common than venous thrombosis (Kuhle et al, 2004) with the exception of stroke. The estimated yearly incidence of stroke in childhood is between 3–8 per 100,000. (Giroud et al, 1995; Lynch et al, 2002). The highest incidence of 25–35 per 100,000 live births has been reported for neonates (Chalmer, 2005). In addition to its impact on the development of children, stroke also quantitatively plays the most important role.

The reasons for the lower incidences of TE in children compared to adults are not completely understood; an intact vascular endothelium, the lower capacity of thrombin generation (Haidi et al, 2006) and elevated levels of α -2-macroglobulin, an inhibitor of thrombin, are possible age-dependent modifying factors in children. There are two age-related peaks in the frequency of thromboembolic disorders in children and adolescents: the first peak corresponds to the perinatal/neonatal period, with the highest relative incidence, and the second is observed post puberty in adolescents, with a higher frequency in females.(Kuhle et al, 2004; Stein et al, 2004).

The relatively higher incidence in neonates as compared to older children may be due to higher hematocrit, and the greater lability of the hemostatic system in neonates due to the generally decreased levels of both coagulation factors and their inhibitors in this age group, except factor VIII (FVIII) and von Willebrand factor (VWF) which are normal or even elevated.(Monagle et al, 2006) In adolescents the incidence equals that of young adults, probably due to the hormonal status, the use of contraceptives or pregnancy in young women, obesity and smoking.(Stein et al, 2004).

Clearly, these epidemiological data have to be considered when assessing the individual absolute thrombotic risk of children with thrombophilia.

3.2 Diagnosis

3.2.1 Clinical presentation

Pain, swelling and discoloration of extremities are acute symptoms of deep vein thrombosis (DVT). Vena cava inferior thrombosis manifests with prominent cutaneous veins and possibly liver or renal dysfunction depending on the site and extension of the thrombus. Superior vena cava thrombosis leads to cyanosis and swelling of the head and upper thorax with prominent collateral veins and may finally result in acute cardiac failure. Portal vein thrombosis, in most cases due to central catheters, and renal vein thrombosis with hematuria as a frequent sign may result in functional impairment or even failure of liver and renal function, respectively. Acute chest pain and dyspnea could suggest pulmonary embolism. Acute headache, visual impairment, cerebral convulsions and signs of venous congestion may indicate sinus venous thrombosis. Signs and symptoms of central venous catheter (CVC)-associated DVT are loss of CVC patency, the need for local thrombolytic therapy or CVC replacement, CVC-related sepsis, or prominent collateral circulation over chest, neck and head.

Childhood arterial ischemic stroke (AIS) manifests in neonates preferentially with seizures and abnormalities of muscle tone, whereas in elder children hemiparesis is the most frequent neurologic sign.(Steinlin et al, 2005) Acquired or inherited severe deficiencies of protein S and protein C are disorders involving both the microcirculation and arterial vessels and may manifest with characteristic symptoms such as deep skin necrosis (purpura fulminans), blindness due to retinal vessel occlusion and arterial embolism followed by necrosis of distal extremities or whole limbs. Thrombotic thrombocytopenic purpura (TTP), a severe microangiopathic disorder is characterized by nonimmunologic hemolytic anemia and thrombocytopenia, neurologic symptoms, and renal, pulmonary and cardiac involvement.

3.2.2 Laboratory parameters

Every thrombotic event initiates a particular response to re-establish the balance of the hemostatic system, e.g., by fibrinolysis. Subsequently markers of fibrinolysis such as D-

dimers can be detected in the circulation. The specificity of these markers is low; however, the negative predictive value of the D-dimer test to correctly exclude DVT is as high as 89% in adult patients with likely DVT compared to 99% in patients who were categorized as unlikely to have DVT. (Wells et al, 2003) In a study on the outcome of TE in children, elevated D-dimer and/or FVIII:C were found in only 67% of the patients; however, elevation of these markers at diagnosis and during follow-up are significantly correlated with persistence or recurrence of TE and/or a post-thrombotic syndrome. (Goldenberg et al, 2004)

3.2.3 Imaging

Color Doppler ultrasound, conventional and MRI angiography, lineograms and echocardiography are the diagnostic means of imaging the occlusion of vessels. Pulmonary embolism of proximal pulmonary arteries can be visualized by echocardiography and by CT scan; however, the specificity and sensitivity are low in detecting more distal clots. In such cases ventilation and perfusion scintigraphies are the recommended techniques for children. (Babyn et al, 2005) Transcranial Doppler ultrasound is used to assess the risk of stroke in patients with sickle cell disease. All techniques can be regarded as equally specific, sensitive and precise; their application, however, differs with respect to the region of interest, age and therapeutic options. **Table 3** lists the different techniques with respect to their application.

Method	Indication	Limitations
Lineograms	CVC related thrombosis	Only clots at the tip of the CVC and the distal adjacent vessel wall
Color Doppler ultrasound	DVT, SVT*	Exception: subclavian vein, use venography
Bilateral venography	DVT, SVT	Exception: jugular vein, use color Doppler ultrasound conventional or MRI
Echocardiography	CVC-related thrombosis, intracardial thrombus, pulmonary embolism	Distal clots in PE
Scintigraphy	Pulmonary embolism	—
Abbreviations: CVC, central venous catheter, DVT, deep vein thrombosis, SVT, Sinus venous thrombosis		
* in young infants through the patent fontanella.		

Table 3. Imaging methods for Thromboembolism in neonates and children.

3.3 Prothrombotic risk factors

Assessment of prothrombotic risk factors is by no means suitable for diagnosing TE. It may possibly help to explain unusual manifestations of TE; however, the predictive power concerning outcome, thereby providing a basis for therapeutic and prophylactic decisions is still a matter of ongoing studies and debate. Interpretation of laboratory data is strongly age dependent since normal ranges may differ considerably between newborns, young children and adolescents.

3.3.1 Hereditary prothrombotic factors

The most important factors involved in the genetic predisposition to thrombophilia are the factors of the coagulation cascade and in particular their natural inhibitors. It is not clear if

genetic defects of fibrinolysis also contribute to the hypercoagulable state. Certain metabolic defects also cause thrombophilia.

3.3.1.1 Coagulation factors

3.3.1.1.1 Fibrinogen (FI)

In addition to being the final substrate for thrombin, FI is also an acute-phase protein that may lead to acquired thrombophilia and may also contribute to the risk of arterial TE. (Rothwell et al, 2004) Genetic defects causing dysfibrinogenemia associated with thrombophilia are rare.

3.3.1.1.2 Prothrombin (FII)

Heterozygosity for the 20210A allele of the common FII polymorphism 20210G/A in the untranslated 3' region of the Prothrombin (FII) gene (Poort et al, 1996) is found at a prevalence of 2.7% in the normal Caucasian population ($n = 11,932$, cumulative data from several studies). This mutant correlates with slightly elevated FII levels, suggesting a quantitative contribution to thrombophilia, and is found at a frequency of 7.1% in unselected patients with thrombosis ($n = 2884$, cumulative data from several studies). The derived relative risk for thrombosis is 2.6. FII 20210A also seems to play a role in childhood stroke. Published data, however, do not give a clear picture. (Nowak - Gottl et al, 1999; Kenet et al, 2000) At least, FII 20210A does not seem to be involved in re-infarction. (Kurnik et al, 2003).

3.3.1.1.3 Factor V (FV)

The FV mutation Arg506 to Gln506 (R506Q or FV Leiden) causes relative resistance against cleavage by the activated protein C (PC) complex. (Dahlbäck et al, 1993; Bertina et al, 1994) It has been identified as the most common significant genetic risk factor for thrombosis to date. The prevalence in the normal Caucasian population is on the average 5%, with prevalences in particular populations of up to 15%. (Zoller et al, 1996) The relative thrombotic risk for heterozygotes is 6- to 8-fold, whereas homozygotes carry an 80-fold relative risk. (Koster et al, 1993) In children with venous thrombosis, FV Leiden was identified in up to 30% (Aschka et al, 1996) In contrast to adults it may also play a role in childhood stroke. (Nowak - Gottl et al, 1999)

3.3.1.1.4 Factor VIII (FVIII)

Elevated FVIII seems to contribute to the risk of TE in children. Furthermore, persistence of elevated FVIII after TE may also predict an unfavorable prognosis (Goldenberg et al, 2004), see Laboratory parameters.

3.3.1.1.5 Von Willebrand factor

Due to its key position in platelet adhesion and aggregation under conditions of high shear forces, VWF plays a most important hemostatic role in arterial vessels and in the microcirculation. (Ruggeri, 2004) This suggests a significant contribution of VWF to arterial TE and to microangiopathies such as thrombotic thrombocytopenic purpura (TTP). An elevated level of VWF is an independent risk factor for myocardial infarction and stroke in adults. (Vischer, 2006) It has not yet been shown whether elevated VWF also plays a role in arterial thrombosis of childhood. In the neonate, supra large VWF multimers, which are the most active in primary hemostasis, are more abundant than later in life and correlate with a

very effective platelet dependent function of VWF in newborns.(Rehak et al, 2004) It can be speculated if these large multimers contribute to the higher rate of stroke in the perinatal period, but respective data have not been reported yet. However, it is now clear that supra large VWF multimers are responsible for the life-threatening condition of TTP (Lammle et al, 2005).

3.3.1.2 Inhibitors of hemostasis

The hemostatic process is tightly regulated by specific inhibitors that act on coagulation factors and on the factors of primary hemostasis. Functionally most important are tissue factor pathway inhibitor, the PC system, antithrombin (AT) and the VWF cleaving protease ADAMTS13. Clinically, to date only the latter three are important. Involvement of the coagulation inhibitors AT, PC and Protein S (PS) is rare with a prevalence in unselected patients with thrombosis of 0.019 for AT, 0.037 for PC, and 0.023 for PS deficiency.(Pabinger & Schneider, 1996; Koster et al, 1995) Recently, severe deficiency of ADAMTS13 has been identified as the causative factor of the rare TTP in most TTP patients (Lammle et al, 2005).

3.3.1.2.1 Protein C system

The PC system comprises PC, PS and FV as co-factors. PC is activated to APC by thrombin, which changes its substrate specificity from FI to PC by being bound to thrombomodulin at the endothelial cell surface. APC cleaves and inactivates aFV and aFVIII at specific proteolytic sites, thereby regulating the formation of thrombin. Severe PC deficiency as well as severe PS deficiency correlates with purpura fulminans, a life-threatening thromboembolic disorder of the microcirculation and larger vessels. Heterozygous deficiency of either inhibitor correlates with venous TE. PC also binds plasminogen activator inhibitor 1 (PAI1) which then facilitates fibrinolysis. This dual function of PC suggests a central role in the regulation of thrombus formation.

3.3.1.2.2 Antithrombin

When bound to heparan sulfate on endothelial cells, AT inhibits thrombin but also aFXI, aFIX and aFX. Its action on thrombin is enhanced 1000-fold by heparin through an allosteric conformational change. In contrast, low-molecular-weight heparin makes AT more aFX specific. These effects are the basis for prophylactic or therapeutic anticoagulation by heparin. Even mild hereditary deficiency of AT function may correlate with thrombophilia with a penetrance higher than in PC and PS deficiency.

3.3.1.2.3 ADAMTS13

ADAMTS13 regulates the size of VWF multimers and thereby its functional activity in primary hemostasis. Its deficiency has clearly been assessed as playing the causative role in TTP.(Lammle et al, 2005) An acquired form, caused by autoantibodies against ADAMTS13, and an inherited form called Upshaw Schulman syndrome (USS) due to mutations in the gene, exist. Lack of the protease correlates with persistence of supra large VWF multimers and, on an adequate trigger (infection, stress, hypoxia), these large multimers will induce platelet adhesion and aggregation in the microcirculation with subsequent microangiopathy, finally resulting in organ failure and death in 80% of cases when untreated. Thrombosis of larger venous and arterial vessels has also been observed. In childhood, TTP is rare and seems more often inherited.(Schneppenhim et al, 2004) Oligo-symptomatic courses have

been observed, however, their long-term prognosis is not clear. In addition to the obvious causative role of severe ADAMTS13 deficiency in TTP, the impact of milder ADAMTS13 deficiency as thrombophilic factor has not been assessed yet, but is subject of ongoing studies. ADAMTS13 has been identified as a potent antithrombotic in an animal model, (Chauhan et al, 2006) which may be of future therapeutic interest.

3.3.1.3 Metabolic conditions

3.3.1.3.1 MTHFR polymorphism 677C/T

The rare condition of classical homocystinuria is most often caused by a deficiency of either cystathionine- β -synthetase or 5-methyltetrahydrofolate-homocysteine-methyltransferase and correlates with frequent TE due to severe homocysteinemia causing endothelial cell damage. The activity of 5-methyl tetrahydrofolate-homocysteine-methyltransferase in turn depends on the availability of 5-methyl-tetrahydrofolate, regulated by 5, 10-methyl tetrahydrofolate-reductase (MTHFR). A common thermolabile MTHFR-variant (MTHFR, 677C>T) correlates with a slightly elevated level of homocysteine. Although repeatedly claimed in many studies, this variant does not seem to be an independent risk factor for TE.

3.3.1.3.2 Lipoprotein (a)

Lipoprotein (a) is considered a significant venous and arterial risk factor for TE in children.(Nowak - Gottl et al, 1999; Nowak - Gottl et al, 1999) However, other reports could not confirm these findings.(Revel - Vilc et al, 2003) Levels of Lp(a), though genetically determined, vary considerably among different populations. Lp(a) has structural homology to plasminogen, suggesting a possible competitive mechanism of Lp(a) in fibrinolysis. However, the lack of correlation between severe plasminogen deficiency and TE speaks against this hypothesis.

3.3.2 Acquired prothrombotic risk factors

3.3.2.1 Central venous catheters

CVCs have become critically important as medical and supportive management of various diseases and have greatly improved quality of life. They bear two serious complications: thrombotic occlusion and CVC-associated DVT as well as systemic infections. CVCs seem to be the most important risk factor for DVT. The range of reported CVC-related DVT ranges from 1% to nearly 70%, reflecting the problem of different definitions, diagnostic methods and alertness.(Mitchell et al, 2003; Male et al, 2003) However, the estimated contribution of CVCs to all thromboembolic events in newborns is as high as 90% and over 50% in older children.(Parasuraman & Goldhaber, 2006) There are only a few controlled studies on the prevalence of CVC-related DVT and infection rate as well as the efficacy of antithrombotic measures to prevent catheter occlusion and infection.

3.3.2.2 Childhood cancer

TE is a well known complication in adult patients with cancer. With the exception of acute lymphoblastic leukemia (ALL), the knowledge about TE in childhood cancer is still limited. ALL has the highest rate of TE in childhood that is not necessarily related to the use of a CVC. In contrast, brain tumors have a rather low incidence of thrombosis with or without CVC.(Tabori et al, 2006) An overall estimation looks at a risk of up to 16%.

TE in cancer is the result of complex interactions of a variety of factors such as the malignancy itself, chemotherapy and its side effects including infections or dehydration, CVCs, the unbalanced hemostatic system with predominant hypercoagulability as well as possible hereditary thrombophilia. The impact of the different types of childhood malignancy on the hemostatic system is still not well understood. Most reports are regarding ALL and show the highest risk for TE under ALL/non-Hodgkin lymphoma (NHL) treatment is during induction and re-induction therapy that contains L-asparaginase, the most common site being the upper deep venous system and the cerebral veins.

3.3.2.3 Thrombosis and antiphospholipid syndrome (APS)

APS is an antibody-mediated thrombophilic state characterized by specific clinical manifestations of venous, arterial or small vessel TE at any site as well as the presence of antiphospholipid antibodies (APA) in the blood. In addition to DVT, acute ischemic stroke or transient ischemic attack are characteristic. APS is often associated with a number of autoimmune disorders.(Miyakis et al, 2006) APS in women causes adverse pregnancy outcome including unexplained still birth or prematurity because of severe placental insufficiency (multiple infarction) or severe (pre)eclampsia. APS is classified as primary and secondary; the clinical picture, however, is the same. Patients with no underlying disease are diagnosed as primary APS. Secondary APS refers to patients with underlying autoimmune (mainly rheumatologic) disorders as well as viral and bacterial infections or cancer.

All proposed pathophysiological mechanisms share the binding of the APA to anionic protein-phospholipid-complexes, leading to activation of endothelial cells, platelets and prothrombin, interference with natural inhibitory pathways and fibrinolysis, and disruption of the binding of annexin V to phospholipids coating the vascular system.(Levine et al, 2002; Rand, 2003) There are clinical/laboratory diagnostic and therapeutic criteria for adults (Miyakis et al, 2006) that do not apply equally for children. There have been recent reports on gene expression profiles to identify subtle distinctions in order to define the clinical relevance of different APA.(Ortel, 2006; Ortel, 2006) Apart from DVT as the most frequent clinical symptom in children along with the presence of LAC and high risk of recurrence without adequate long-term anticoagulation, there is a subgroup of children presenting with perinatal stroke and no risk of recurrence independent of secondary antithrombotic prophylaxis.(Kenet, 2006)This underlines the discordance to adults and the need for diagnostic and therapeutic guidelines to be defined for pediatric patients.

APA along with decreased activity of various coagulation factors, mainly F XII, are found in about 50% of otherwise healthy children with multiple viral infections, screened for prolonged a PTT preceding tonsillectomy or adenotomy.4244 APA in this context are in association to the repeated infections and do not appear to be clinically relevant, carry no risk for bleeding or TE, and hence do not influence perioperative management. They usually disappear after tonsillectomy and/or with decreasing frequency of infectious episodes. In contrast, life-threatening TE including purpura fulminans may occur with varicella, which have been shown to have a increased prevalence of APA and associated PS deficiency.(Manco - Johnson, 1998) Bleeding is rare and responds to corticosteroids.

3.3.2.4 Heparin - induced thrombocytopenia type 2 (HIT)

The overall incidence of HIT type 2 is estimated around 1% of patients hospitalized in pediatric intensive care units.(Klenner et al, 2004; Newall et a, 2003) Most often it is observed in neonates and infants after cardiac surgery and in adolescents treated with unfractionated

heparin (UFH) for venous thrombosis. HIT-associated TE is mainly venous but arterial events may occur.

3.3.2.5 Other acquired prothrombotic conditions

Perinatal asphyxia, systemic infections/sepsis/DIC, congenital heart disease (CHD) and hypovolemia are the main risk factors in neonates, the latter particularly prone to arterial events in association with CHD and/or arterial catheters frequently used in an intensive care setting.⁴⁷ There are additional factors in older children: trauma, major surgery, immobilization, estrogen containing contraceptives in adolescent girls, corticosteroid therapy, nephrotic syndrome, hemolytic uremic syndrome, inflammatory bowel disease, and rheumatic and other chronic disorders. To date, it remains an individual decision if and which antithrombotic prophylaxis should be offered considering additional and individual risk factors.

3.4 Therapy and prophylaxis

Irrespective of an underlying disease, every thromboembolic manifestation should be treated, aiming at the complete recanalization of the occluded vessel and stopping the thrombotic process. In the vast majority of cases thrombosis will resolve under heparin given for 5–14 days. Other therapy options with a higher risk such as thrombolytic therapy or surgical embolectomy should be limited for patients with extensive thrombosis and/or threatened organ function. As LMWH show considerable advantages over UFH for therapeutic as well as prophylactic purposes, the following recommendations are in favor of LMWH. Yet evidence shows no difference in the antithrombotic efficacy. For detailed recommendations refer to **Table 4** and reference (Monagle et al, 2004).

UFH i.v.	Neonates < 5kg	Children > 5kg	Target aPTT at 4h
loading dose	1 x 75 U/kg/10 min	1 x 75 U/kg/10 min	
maintenance	25–30 U/kg/h	20 U/kg/h	60–85 sec.
LMWH s.c.	Neonates < 5kg	Children > 5kg	Target anti-FXa at 4 h
initial treatment dose			
Enoxaparin*	1 x 2.0 mg/kg/d	1 x 1.5 mg/kg/d	0.4–0.8 U/mL
Dalteparin	1 x 200 U/kg/d	1 x 150 U/kg/d	0.4–0.8 U/mL
Reviparin	2 x 150 U/kg/d	2 x 100 U/kg/d	0.5–1.0 U/mL
initial prophylactic dose			
Enoxaparin*	1 x 1.5 mg/kg/d	1 x 1.0 mg/kg/d	< 0.4 U/mL
Dalteparin	1 x 100 U/kg/d	1 x 50 U/kg/d	< 0.4 U/mL
Reviparin	2 x 50 U/kg/d	2 x 30 U/kg/d	< 0.5 U/mL

* 1 mg Enoxaparin = 110 anti-FXa units

For UFH: aPTT 4 hours after loading dose and 4 hours after each dosage adjustment, at least once daily; keep AT level within normal range; daily blood count (platelets!). For LMWH: anti-FX activity 4 hours after injection

Table 4. Recommended dosing of UFH and LMWH in neonates and children.

Recommendations

In children with VTE (CVL and non-CVL related): first TE for children:

In children with thrombosis, we recommend anticoagulant therapy with either UFH or LMWH (Grade 1B).

Remark: Dosing of IV UFH should prolong the aPTT to a range that corresponds to an anti-FXa level of 0.35 to 0.7 U/mL, whereas LMWH should achieve an anti-FXa level of 0.5 to 1.0 U/mL 4 h after an injection for twice-daily dosing.

We recommend initial treatment with UFH or LMWH for at least 5 to 10 days (Grade 1B). For patients in whom clinicians will subsequently prescribe VKAs, we recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the INR has not exceeded 2.0 (Grade 1B). After the initial 5- to 10-day treatment period, we suggest LMWH rather than VKA therapy if therapeutic levels are difficult to maintain on VKA therapy or if VKA therapy is challenging for the child and family (Grade 2C).

We suggest children with idiopathic TE receive anticoagulant therapy for at least 6 months, using VKAs to achieve a target INR of (INR range, 2.0 to 3.0) or alternatively using LMWH to maintain an anti-FXa level of 0.5 to 1.0 U/mL (Grade 2C).

Recurrent Idiopathic TE for Children

Recommendations

For children with recurrent idiopathic thrombosis, we recommend indefinite treatment with VKAs to achieve a target INR of 2.5 (INR range, 2.0–3.0) [Grade 1A].

Remark: For some patients, long-term LMWH may be preferable; however, there are little or no data about the safety of long-term LMWH in children.

Recurrent Secondary TE for Children

Recommendations

For children with recurrent secondary TE with an existing reversible risk factor for thrombosis, we suggest anticoagulation until the removal of the precipitating factor but for a minimum of 3 months (Grade 2C). In addition, with specific respect to the management of CVL-related thrombosis: 1.2.8. If a CVL is no longer required, or is nonfunctioning, we recommend it be removed (Grade 1B). We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal (Grade 2C). If CVL access is required and the CVL is still functioning, we suggest that the CVL remain *in situ* and the patient be anticoagulated (Grade 2C).

For children with a first CVL-related DVT, we suggest initial management as for secondary TE as previously described. We suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5–1.9) or LMWH (anti-FXa level range, 0.1 to 0.3) be given until the CVL is removed (Grade 2C). If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVL is removed but at least for a minimum of 3 months (Grade 2C).

Use of Thrombolysis in Pediatric Patients With DVT.

Recommendations

In children with DVT, we suggest that thrombolysis therapy not be used routinely (Grade 2C). If thrombolysis is used, in the presence of physiologic or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (Grade 2C).

Thrombectomy and IVC Filter Use in Pediatric Patients With DVT.

Recommendations

If life-threatening VTE is present, we suggest thrombectomy (Grade 2C).

We suggest, following thrombectomy, anticoagulant therapy be initiated to prevent thrombus reaccumulation (Grade 2C).

In children \leq 10 kg body weight with lower-extremity DVT and a contraindication to anticoagulation, we suggest placement of a temporary IVC filter (Grade 2C).

We suggest temporary IVC filters should be removed as soon as possible if thrombosis is not present in the basket of the filter and when the risk of anticoagulation decreases (Grade 2C).

In children who receive an IVC filter, we recommend appropriate anticoagulation for DVT (see 1.2) as soon as the contraindication to anticoagulation is resolved (Grade 1B).

Pediatric Cancer Patients With DVT

Use of Anticoagulants as Therapeutic Agents

Recommendations

In children with cancer, we suggest management of VTE follow the general recommendations for management of DVT in children.

We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (eg, use of asparaginase) [Grade 2C].

Remark: The presence of cancer, and the need for surgery, chemotherapy or other treatments may modify the risk/benefit ratio for treatment of DVT, and clinicians should consider these factors on an individual basis.

Use of Anticoagulant as Thromboprophylaxis

Recommendations

We suggest clinicians not use primary antithrombotic prophylaxis in children with cancer and central VADs (Grade 2C).

3.4.1 Commonly used anticoagulants

3.4.1.1 Unfractionated heparin

The following disadvantages should be considered: the need for venous access for therapy and monitoring, age-dependent unpredictable pharmacokinetics; normal AT levels required; monitoring by a PTT prone to pre-analytic errors; risk for bleeding; risk for HIT. Intravenous UFH should only be given in the initial phase of antithrombotic therapy and then switched to LMWH.

3.4.1.2 Low - molecular - weight heparin

Advantages are easy subcutaneous administration once daily without need of venous access, predictable pharmacokinetics, minimal monitoring, minimized bleeding complications, reduced risk of HIT. Infants $<$ 5 kg required about 50% higher doses than older children to reach equivalent anti-FXa levels.(Sutor et al, 2004) As a general guideline

we recommend LMWH with therapeutic anti-Xa levels for 4–6 weeks, followed by prophylactic dosage up to ≤ 6 months. For the treatment duration of different sites, types and age groups refer to references (Monagle et al, 2004; Andrew et al, 2000).

3.4.1.3 Thrombolytic agents

The agent of choice is rt-PA. Streptokinase should not be used because of its allergic reactions. The use of urokinase at least in the USA is restricted for safety concerns. rt-PA may be indicated if thrombosis is extensive or organ/life threatening. The established contraindications in adults apply for children as well but should be considered relative.⁵³ Therapeutic recommendations are listed in **Table 5**.

Contraindications			
Strong	within 10 days after hemorrhage or major surgery within 7 days after severe asphyxia		
Soft	within 3 days after invasive procedure within 48 hours after cerebral convulsion prematurity < 32 weeks of gestation sepsis active minor hemorrhage refractory thrombocytopenia and hypofibrinogenemia		
Therapy	Loading Dose	Maintenance	Monitoring
rt-PA	0.1–0.2 mg/kg/10 min.	0.8–2.4 mg/kg/24 h	FI, platelets, D-dimers
UFH	none	5–10 U/kg/h	Apt
Indications: extensive and/or life/organ-threatening thrombosis. Contraindications: on an individual basis to be considered relative, not absolute; keep fibrinogen > 0.5 g/L and platelets > 50 g/L; increasing D-dimers indicate effective fibrinolysis; dose reduction or cessation of rt-PA if major bleeding occurs; minor bleeding (oozing from catheter puncture site or wound) treat with local pressure; optimal duration of rt-PA therapy uncertain, mostly up to 7 days, shorter/longer courses			

Table 5. Recommendations for systemic thrombolysis in neonates and children

3.4.1.4 Vitamin K antagonists

OAC	Day 1	Day 2	From Day 3	Target INR
Phenprocoumon	6 mg/m ²	3 mg/m ²	1–2 mg/m ²	2.0–3.0
Warfarin	0.2 mg/kg	0.2 mg/kg	0.1–0.3 mg/kg	2.0–3.0
Reversal of oral anticoagulant therapy				
no bleeding, slow reversal	vitamin K 0.5–2.0 (–5.0) mg orally (s.c., i.v.)			
no bleeding, rapid reversal	vitamin K 0.5–2.0 (–5.0) mg s.c. or i.v.			
significant bleeding, not life threatening	vitamin K 0.5–2.0 (–5.0) mg s.c. or i.v. + FFP 20 mL/kg			
significant bleeding, life threatening	vitamin K 5 mg i.v. over 20 min. (risk of anaphylactic shock) + prothrombin concentrate (Prothomplex) 50 U/kg i.v.			
Coumarin therapy always to begin with concomitant heparin therapy (UFH or LMWH); to stop heparin, INR within therapeutic range for 2 days, concomitant medication at least 5 days; attention to multiple drug interactions				

Table 6. Recommended dosing of oral anticoagulants (OAC) in neonates and children.

Warfarin and phenprocoumon are usually administered for oral anticoagulation and inhibit g-carboxylation of vitamin K-dependent proteins. Considerable variation due to nutrition, co-medication, intercurrent illness and difficult monitoring requires close supervision and dose adjustment. We administer vitamin K antagonists in cases of prophylaxis exceeding 6 months (Table 6).

3.4.1.5 Infusion of deficient inhibitors of hemostasis

In cases of thrombosis with hereditary or acquired deficiencies of coagulation inhibitors, replacement therapy may be an option. Concentrates of AT and PC are commercially available and are life saving in conditions of purpura fulminans due to inhibitor deficiency. PC concentrate also proved to be effective in heterozygous or acquired PC deficiency. Fresh frozen plasma is the only but effective option of treating patients with purpura fulminans or hereditary TTP due to PS or ADAMTS13 deficiency, respectively.

3.4.2 New anticoagulants

The limitations of the traditional anticoagulants are particularly obvious in pediatrics; hence, the promotion of the new drugs already approved in adults urgent. Yet there is but individual experience in children with the following substances: the pentasaccharides fondaparinux and idraparinux, and the direct thrombin inhibitors hirudin, bivalirudin, argatroban; ximelagatran has been withdrawn from the market because of hepatic toxicity.(Balsa, 2005; Kuhle et al, 2006).

3.4.3 Special conditions

3.4.3.1 Prophylaxis of CVC occlusion

3.4.3.1.1 UFH

Prophylactic UFH seems to significantly decrease CVC-related DVT as well as bacterial colonization of the catheter.(Hentschen & Sutor, 2002) Heparin-bonded catheters do not reduce clot formation and bacterial colonization beyond 24 hours after CVC insertion.

3.4.3.1.2 Thrombolytic agents (urokinase, rt - PA)

Thrombolytic therapy is widely and safely used for the management of occluded catheters. There are only a few studies using thrombolytic agents prophylactically in order to reduce catheter infections and occlusions. Some studies show a substantial benefit of thrombolytic agents over UFH or no prophylaxis.(Hentschen & Sutor, 2002) whereas others get contradictory results.(Aquino et al, 2002; Solomon et al, 2000)

3.4.3.1.3 LMWH

Prophylactic use of LMWH has been efficient and safe in the treatment and prevention of DVT in children with cancer.(Elhasid et al, 2001; Massicotte et al, 2003; Tabori et al, 2006) However, LMWH to maintain CVC-patency and prevent CVC-related DVT has to remain an individual decision. For the recommended dosage see Table 4.

3.4.3.1.4 Oral anticoagulation with vitamin K - antagonist

There are no data for children on using low-dose oral anticoagulation to prevent CVC-associated DVT and to maintain catheter patency. Considering the heterogeneous pediatric

population requiring a CVC with respect to age, thrombogenic risk profile, underlying disease, intensity and duration of treatment, the use of vitamin K-antagonists must remain a decision on a strictly individual base.

3.4.3.2 Management of Thrombosis in children with cancer

The main challenge is to keep the balance of benefit and risk of an antithrombotic treatment, as most children are being treated with chemotherapy with intermittent thrombocytopenia and an unbalanced hemostatic system, both of which lead to potential bleeding complications. It is therefore strongly recommended not to use antithrombotic agents with potentially serious side effects such as thrombolytic agents, UFH or vitamin K antagonists.

Recommendations

In children with cancer, we suggest management of VTE follow the general recommendations for management of DVT in children.

We suggest the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (*eg*, use of asparaginase) [Grade 2C].

Remark: The presence of cancer, and the need for surgery, chemotherapy or other treatments may modify the risk/benefit ratio for treatment of DVT, and clinicians should consider these factors on an individual basis.

3.4.3.3 Prophylaxis of TE in children with cancer

Since a high percentage of TE seems to be directly CVC-related, it is of primary importance to maintain its patency. Though there is a lack of clear evidence based indications the following situations for primary prophylaxis may be individually considered: 1) children with hereditary thrombophilia under intensive chemotherapy, 2) adolescents in the presence of additional risk factors such as major surgery or immobilization, 3) patients with prior TE in their history and 4) children with tumors compressing large vessels. Because ALL carries the highest risk for TE an efficient prophylaxis would be of major importance. To date there are no controlled trials that allow the extrapolation of prophylactic strategies. The German BFM-Study Group is conducting the first randomized interventional trial comparing three different antithrombotic strategies during ALL-induction therapy (Thrombotect). This ongoing trial is expected to provide the basis for risk adapted prophylaxis guidelines.

3.4.3.4 Antithrombotic therapy for APS

Long-term prognosis depends on the risk of recurrent TE, which seems to be the highest within 6 months of discontinuation of anticoagulation.⁶⁴ Duration and intensity of therapy are still controversial, at least for subgroups. After the first DVT, secondary prophylaxis for 12 months is indicated. Lifelong anticoagulation is to be considered after a very serious first event and recurrent TE with persistence of APA. After arterial TE the optimal secondary prophylaxis remains controversial.^{64,65} In children consideration should be given to performing and/or extending first/second line antithrombotic treatment on an individual basis, depending on the presence of underlying disorders.

Recommendations

For children with VTE, in the setting of APLA (*Antiphospholipid Antibodies*), we suggest management as per general recommendations for VTE management in children.

Remark: Depending on the age of the patient, it may be more appropriate to follow adult guidelines for management of VTE in the setting of APLA.

3.4.3.5 Treatment - related indications for Thrombophilia Screening

It makes a difference if children are diagnosed and treated as study patients or if they are individually seen. In the latter case, laboratory work-up of thrombosis in childhood should pertain to the following basic questions: i) is there a specific therapy and ii) what are the consequences of a particular finding concerning future management and counseling of the patient and the family? (Sutor, 2003) Keeping this in mind, the necessary investigations are only a few (see **Table 7**) which is at odds with the current recommendations published by the Subcommittee on Perinatal/Pediatric Hemostasis of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH). (Manco - Johnson et al, 2002) However, since there is no consensus on management guidelines yet, laboratory testing may also vary between different institutions. It is well accepted that the coagulation inhibitors AT, PC and PS should be part of the diagnostic program. Though rare, their deficiencies can be compensated for by commercially available concentrates (AT, PC) and by fresh frozen plasma (PS). In cases of TE accompanied by hemolytic anemia and thrombocytopenia, Upshaw Schulman syndrome should be suspected and ADAMTS13 activity should be determined, since fresh-frozen plasma (FFP) is a life-saving replacement therapy in this condition and plasma exchange is the method of choice in the acquired form. Fasting homocysteine may be determined, since its elevation can be treated by folic acid substitution. However, two recent studies on lowering homocysteine by folate administration in patients with vascular disease did not show a reduction of re-infarction or stroke in adults.(Lonn et al, 2006; Ho et al, 2006) HIT type 2 should be ruled out in patients with thrombosis who show a drop of the platelet count under heparin administration. APA should be determined, since the respective patients require a longer lasting prophylaxis against a relapse. There is no specific treatment for patients with Factor V Leiden or PT G20210A. Although these established hereditary risk factors are the most common, therapeutic and prophylactic measures are not necessarily different for children with or without these risk factors. Indeed, many studies on adults and a few on children have shown that these factors have only minor or even no impact on re-TE in unselected patients with or without these risk factors.(Kurnik et al, 2003; Ho et al, 2006)

1	2	3
Antithrombin	APC resistance (FV Leiden)	PAI-1 polymorphism
Protein C	Prothrombin G20210A	Plasminogen
Protein S	Lipoprotein (a)	Heparin-cofactor II
Antiphospholipid-Ab	Dysfibrinogenemia	FIX
Homocysteine	FVIII	FXI
HIT Type 2	D-Dimer	FXIII
ADAMTS13		VWF
Column 1: factors of therapeutic and/or prognostic relevance; column 2: established risk factors with possible therapeutic and prognostic relevance for the individual patient; column 3: potential thrombophilic factors. Their therapeutic and prognostic relevance for the individual patient is doubtful. Laboratory tests for HIT type 2 and ADAMTS13 are only indicated when additional data suggest their involvement (see text).		

Table 7. List of relevant, established and potential thrombophilic factors

As some studies have suggested, combined thrombophilic factors may enhance the risk of thrombosis. However, the risk of a second event in unselected patients does not seem to be high enough to justify more intense and prolonged anticoagulation, compared to patients without these risk factors. Deviations from this "minimalistic" diagnostic approach may be indicated with respect to the individual case and to the particular institutional management guidelines. Many other factors are part of diagnostic programs, although their contribution to the thrombotic risk seems to be very low or even absent.

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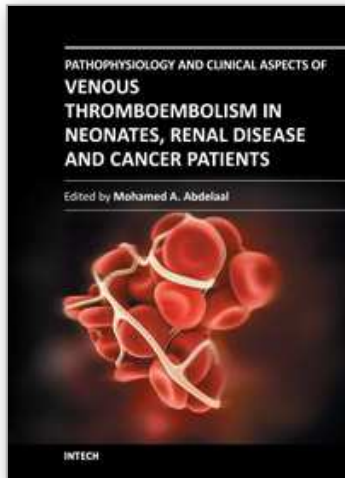
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Venous Thromboembolism remains a major health challenge in many countries because of the morbidity and mortality it inflicts, mainly in hospitalized patients. This book, with contributions from distinguished experts in the field, depicts some hot aspects on aetiologies of VTE, the disease burden in neonates, renal disease and cancer patients as well as issues relevant to prophylaxis and the concept of VTE as patient injury content.

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