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Review Article

Assessment of pediatric vascular thrombosis (as a review of literature)

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Abstract:

Background: Thrombosis is often underdiagnosed in neonates and toddlers. Thrombosis primarily occurs in the pediatric demographic prior to 1 year of age and during adolescence. Thrombosis is the abnormal formation of a clot from blood constituents within a vessel. It results from the disruption of the complex balance of the procoagulant, anticoagulant, and fibrinolytic systems. The morbidity and mortality rates are high, although it occurs less frequently than adult thrombosis and does not present without a triggering event.

Objective: The aim of this review was to identify risk factors, clinical pattern, outcome of thrombosis in children

Methods: A comprehensive search was conducted from April, 2023 to September, 2024 in PubMed, Google Scholar and Science Direct, from January 2000 to September 2025, using the key words: pediatric vascular thrombosis, arterial thrombosis, venous thrombosis, thrombophilia. The reviewers evaluated relevant literature references as well. Only the most recent or complete study was taken into account. Examples of articles that weren't regarded as significant scientific research include unpublished manuscripts, oral presentations, conference abstracts, and dissertations. The lack of resources for translation has led to the ignoring of documents written in languages other than English. The inclusion criteria of the research included studies with children age from one day to 18 years and diagnosis of vascular thrombosis documented by clinical picture and venous doppler study or radiological study and the exclusion criteria was studies with persons above 18 years old.

Results: Both acquired and hereditary factors contribute to the development of pediatric thrombosis. The probability of thrombosis may increase in individuals with one or more hereditary thrombophilia factors. Acquired factors have been shown to induce thrombosis more frequently and effectively than inherited causes in pediatric cases. The principal factors influencing genetic predisposition to thrombophilia are the constituents of the coagulation cascade. The clinical manifestation depends on the thrombus's position and dimensions. The presentation may vary from isolated symptoms to severe, life-threatening events. Every thromboembolic event, irrespective of any underlying condition, must be managed to attain complete recanalization of the occluded vessel and to cease the thrombotic process.

Conclusion: Thrombosis may arise from genetic or acquired factors. The aim of thrombosis management is to inhibit the progression of thrombosis, its recurrence, and related mortality.

Key words: Pediatric vascular thrombosis, arterial thrombosis, venous thrombosis, thrombophilia.

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Introduction

Thrombotic episodes in children are still relatively rare, but they are becoming more important as we learn more about the hemostasis system and thromboembolic illnesses in children. There are a variety of prothrombotic diseases and underlying clinical factors that make blood clot formation more likely in newborns and young children. Thrombosis in children is the subject of increasing efforts to improve diagnosis, prevention, and treatment. (1)

Thrombosis is frequently misdiagnosed in infants and toddlers .(2) For children and neonates, the yearly incidence rate of arterial or venous thrombosis is between 2.6 and 6.4 occurrences per 100,000. (3) An increasing number of pediatric intensive care unit (ICU) cases involve thrombosis, which is particularly prevalent among preterm and critically ill newborns. (4)

Types of thrombosis

Arterial thrombosis: There are two main methods in which children could develop arterial thrombosis: with or without catheters. The insertion of an umbilical catheter in a newborn, a peripheral indwelling arterial catheter to monitor blood pressure in the NICU or after surgery, a congenital cardiac defect in a youngster, or any of several other conditions might cause CAT. New data shows that of all catheter types, 20% are umbilical, 24% are indwelling arterial, and 11% are used for cardiac catheterization. (5)

Most cases of non-catheter-related arterial thrombosis (NCAT) have their roots in either inherited or acquired medical conditions. Problems with lipid metabolism or structural anomalies are examples of congenital diseases. Some conditions can develop over time; these include Kawasaki illness, Takayasu arteritis, and blockages in the arteries leading to certain organs, such as the kidneys, liver, or central nervous system (CNS). (5)

Venous thrombosis: The lungs and deep veins are the most common sites of clotting in venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two subtypes of this illness. The formation of a blood clot in a deep vein, typically in the calf, is the initial step in DVT. The risk of this clot spreading to nearby veins increases as the injury progresses. If a fragment of the clot separates and makes its way to the lungs via the bloodstream, pneumonia can develop. (6)

Epidemiology Children and teenagers, especially those younger than one, are at increased risk of thrombosis. Thrombosis in children occurs at a rate of 0.07 to 0.14 cases per 10,000 people in the overall population. Rates reported in the literature for this event are as follows: 5.3% of newborns admitted to hospitals, 0.5% of neonates generally, and 0.24 of children admitted to neonatal intensive care units. From 34 per 10,000 to 58 per 10,000 represents a 70% rise in the current incidence of thrombosis in youngsters. Several variables may be responsible for this, such as the fact that more patients are surviving who were treated very early on, the increased use of catheters, and the fact that interventional procedures encourage the development of thrombosis. (1)

Infants and young children have a more delicate hemostatic system and higher hemoglobin concentrations due to lower levels of coagulation factors and inhibitors. Factor VIII (FVIII) and von Willebrand factor (VWF), which can be normal or elevated, are the sole outliers to this generalization. This could account for the dramatically higher incidence in newborns. Hormonal changes, adolescent pregnancies, obesity, smoking, and the usage of birth control are likely contributing factors to the fact that it is similar in teenagers and young adults (7). Complications including post-thrombotic syndrome and pulmonary embolism can develop from deep venous thrombosis (DVT) in children, even though this condition only occurs in around 10–14 out of 10,000 pediatric hospitalizations annually. (8)

Despite being less common than adult thrombosis and not developing in the absence of a trigger factor, the mortality and morbidity rates are high. Thrombosis recurrence rates of 8.1%, post-thrombotic syndrome frequency of 12.4%, and death rate of 2.2% are all linked to direct venous thromboembolism (VTE).(9)

Pathophysiology of thrombosis

Molecular Pathophysiology: A condition called thrombosis occurs when blood clots form improperly within a blood vessel. Disruption of the complex interaction between the fibrinolytic, anticoagulant, and procoagulant systems causes its manifestation. Thrombosis develops due to three

mechanisms that Virchow observed in 1856: Variations in arterial wall architecture, changes in physiology (rheology, stasis), and variations in coagulation factor and inhibitor blood levels. [9] Arterial thrombosis is mostly caused by endothelial damage and platelet functions, whereas venous thrombosis is mostly caused by stasis and coagulation-fibrinolytic system abnormalities .[10]

Genetic pathophysiology: An increased risk of vein-related embolism (VTE) has been associated with several common genes, including the F5 gene, which codes for factor V. A mutation in this gene known as Factor V Leiden affects around 5% of Caucasians. The mutation doubles the likelihood of thrombus formation because activated protein C, an anticoagulant protease, is less efficient at inactivating this protein .[11]

Genetic prothrombotic risk factors: Having a tendency to thrombosis runs in families and is known as inherited thrombophilia. Hereditary thrombophilia is characterized by early thrombosis onset, recurrent thrombosis, excessive venous thromboembolic events relative to the underlying etiology, or spontaneous thrombosis in the absence of known clinical triggers. In addition, it is possible to see inherited thrombophilia as carrying genetic components that facilitate the occurrence of thrombosis. Thrombosis can occur even in the absence of positive laboratory results, or vice versa. [9]

- **Hereditary thrombotic factors:** An important factor in the inherited propensity to thrombophilia is the components of the coagulation cascade, particularly their natural inhibitors. It is not known how hypercoagulable hereditary fibrinolysis defects contribute to the disease. Metabolic abnormalities are another source of thrombophilia. [12]

1. Coagulation factors

Fibrinogen (FI): As an acute-phase protein, FI not only increases the risk of arterial TE and may induce acquired thrombophilia, but it is also the last component for thrombin. Having a genetic defect that causes dysfibrinogenemia is also present in very few patients with thrombophilia. [13]

Prothrombin (FII): The common FII polymorphism 20210G/A in the untranslated 3′ region of the Prothrombin (FII) gene14 affects 2.7% of the average Caucasian population. This mutation is seen in 7.1% of those who have thrombosis; it is associated with slightly higher levels of FII, which might mean it has a quantitative role in thrombophilia .[14]

Factor V (FV): Mutations in the FV gene, such as R506Q or FV Leiden, which cause Gln506 to replace Arg506, impair the cleavage efficiency of the activated protein C (PC) complex. This is the most common and important of the thrombosis risk factors that have been identified. Thirty percent or more of the children diagnosed with venous thrombosis had this. In contrast to adult strokes, it may have a role in pediatric strokes. [15] Inadequate response to the anticoagulant APC is a sign of the inherited disorder called as Factor V Leiden. Anticoagulant protein C (APC) is an endogenous protein that decreases thrombin generation by cleaving and inactivating procoagulant Factors Va and VIIIa. R (arginine) 306, R 506, and R 679 are the three amino acid sites where APC may cleave and make Factor Va inactive. At nucleotide 1691 of the Factor V gene, a "Factor V Leiden" mutation occurs when guanine is changed to adenine. Because of this mutation, glutamine is predicted to substitute arginine at the cleavage site of APC at position 506 instead.[16]

Factor VIII (FVIII): It seems that an increased risk of TE in children is associated with higher FVIII. Furthermore, if elevated FVIII remains after TE, it might be indicative of a bad prognosis. [11]

Von Willebrand factor: Under conditions of high shear stress, platelets adhere and aggregate, making the hemostatic activity of VWF in microcirculation and arterial arteries vital. This provides strong evidence that VWF plays a key role in microangiopathies such thrombotic thrombocytopenic purpura (TTP) and arterial TE. Myocardial infarction and stroke are more likely to occur in persons with greater VWF levels. The involvement of increased VWF in pediatric arterial thrombosis has not been shown at this time .[17]

Factor XIII (FXIII): The B subunits of protransglutaminase coagulation factor XIII (FXIII) are responsible for transporting the A subunits to plasma. The A subunits are located on

the outside of the protein. Thrombin activates factor XIII when the transglutaminase dissociates and an N-terminal activation peptide (residues 1-37) is cleaved off the A subunit. When calcium is present, B subunits form an FXIII-A dimer. Because it cross-links fibrin's α- and γ-chains and α2-antiplasmin (α2-AP) to fibrin, activating factor XIIIa is essential for clot stabilization as it enhances the clot's resistance to mechanical and proteolytic stressors. (18)

2. Inhibitors of hemostasis

An inhibitory effect on the hemostatic process can be achieved by blocking the action of certain coagulation factors and primary hemostasis factors. In terms of practical importance, the PC system, antithrombin (AT), the inhibitor of the tissue factor pathway, and the VWF cleaving protease ADAMTS13 rank supreme .(19)

Protein C system: In the PC system, PC, PS, and FV all work together as co-factors. Thrombin changes its substrate preference from FI to PC when it binds to endothelial cell surface thrombomodulin, converting PC to APC. Thrombin synthesis is regulated by APC through specific proteolytic sites cleavage and inactivation of aFV and aFVIII. Serious PC and PS deficits are linked to the potentially deadly microcirculation and larger vessel thromboembolic disease purpura fulminans. (20)

Antithrombin: Thrombin, aFXI, aFIX, and aFX are all blocked by AT after endothelial cells bind heparan sulfate. The impact of cheparin on thrombin is enhanced a thousandfold due to an allosteric conformational change. Conversely, when low-molecular-weight heparin is utilized, AT becomes more aFX specific. Both the prophylactic and therapeutic anticoagulant effects of heparin are based on these responses. The penetrance of thrombophilia is higher than that in PC and PS deficits, suggesting that even a little genetic impairment of AT function may be linked to the disorder. (21)

ADAMTS13: The regulation of VWF multimer size is one of the key hemostasis functions of ADAMTS13. Its absence is definitely a role in TTP, that much is certain. Autoantibodies against ADAMTS13 produce the genetic form of Upshaw Schulman syndrome (USS), whereas an acquired variation is also present. Untreated supra large VWF multimers can linger in the bloodstream in the absence of the protease. In response to factors such as infection, stress, or low oxygen levels, they can bind to platelets and aggregate in the microcirculation, causing microangiopathy. In the worst-case scenario, eighty percent of patients die from organ failure. (22)

3. Metabolic conditions

MTHFR polymorphism: Among its functions, methylenetetrahydrofolate reductase controls homocysteine metabolism. More and more research is linking methylation pathways and increased plasma total homocysteine concentrations to atherosclerotic disease and, by extension, venous thrombosis. A number of hypothesized mechanisms have connected total homocysteine to occlusive vascular disease. The thrombogenic effects of homocysteine and its metabolites may be due to its effects on thrombomodulin expression, protein C activation, increased platelet aggregation, and thromboxane production. (23)

Also, homocysteine oxidation can create free radicals and hydrogen peroxide, which can damage the endothelial lining and speed up LDL oxidation—two crucial processes in the formation of atherosclerosis. The significance of the MTHFR enzyme for vascular function becomes abundantly evident when considering the severe hereditary MTHFR deficiency associated with the rare but well-documented homocystinuria syndromes clinical disorders. These diseases include early atherosclerosis, thrombosis, and other neurological abnormalities. (24)

- **C677T polymorphism in the MTHFR gene**

Classical homocystinuria generally occurs due to an inadequate level of either cystathionine-β-synthetase or 5-methyltetrahydrofolate-homocysteine-methyltransferase. Excessive homocysteinemia damages the endothelium cells, which is why this disease is linked to frequent TE. Last but not least, 5-methyl tetrahydrofolate-homocysteine-methyltransferase activity is controlled by 5, 10-methyl tetrahydrofolate-reductase (MTHFR). An MTHFR-variant that is common and thermolabile (MTHFR, 677C>T) is associated with a slightly higher homocysteine level. This variant does not

seem to be a risk factor for TE independently, contrary to assertions made in other studies. [25]
Among the general population, a unique genetic risk factor for cardiovascular disease has been discovered: a common C677T variant in the MTHFR gene. Enzyme activity is approximately 35% lower in T allele carriers than in C allele carriers; this mutation determines a temperature-dependent loss of function. The total plasma homocysteine levels of those with the 677TT genotype were significantly higher than those of heterozygotes or those with wild-type C alleles. [26]

- **A1298C polymorphism in the MTHFR gene**

A second frequent mutation was also found in the same gene. At nucleotide 1298 (A1298C), this new mutation allows the MTHFR protein to undergo a glutamate to alanine substitution. Just like the C677T mutation, the A1298C mutation does not result in a thermolabile protein. However, it does decrease MTHFR activity, and this impact is more pronounced in the homozygous (CC) state than in the heterozygous (AC) or normal (AA) ones. [27]
The A1298C variation of the MTHFR gene may influence MTHFR activity, according to some data. There is evidence that this A1298C polymorphism has a less impact on enzyme activity reduction compared to the 677 mutations. It is more apparent in the homozygous (CC) condition as compared to the normal (AA) or heterozygous (AC) ones. In comparison to those who are just heterozygotes for the C677T variant, the control activity in people who are heterozygotes for both the C677T and A1298C mutations falls between 50% and 60%. One interesting thing that came out of a recent study is that RA is more common in people from Southern Europe who had the A1298C mutation in the MTHFR gene. [28]

Lipoprotein (a)

In children, lipoprotein (a) is one of the main arterial and venous risk factors for TE. However, other research did not support the same findings. Although Lp(a) levels are determined by genes, there is a notable variation among populations. The structural similarity between Lp(a) and plasminogen suggests that the two may compete for fibrinolysis. The fact that TE is not linked to severe plasminogen deficiency, nevertheless, calls this idea into question. [29]

Diagnosis of hereditary thrombophilia

Genetic testing for thrombophilia is a common clinical procedure in individuals with thrombosis or a family history of the disorder. Approximately 5- 10% of the general population and 40% of individuals with a history of venous thromboembolism have inherited disorders that raise the risk of this condition. Therefore, significant organizations like the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Hemostasis (ISTH) pushed for the testing of hereditary thrombophilia in all patients diagnosed with thrombosis from the late 90s, when hereditary factors were initially identified, until the early 2010s. [9]

The value of hereditary thrombophilia tests in children with thrombosis

Common methods for determining if a person has hereditary thrombophilia include antithrombin (AT), protein C (PC), protein S (PS), factor vulnerability (FVL), and PTM testing. To be classified as "low-risk thrombophilia," one must be a carrier of either FVL or PTM, whereas "high-risk thrombophilia" is defined as having either a PC, PS, or AT deficiency, or a mix of all three. The likelihood of venous thromboembolism (VTE) is 8.73 times higher in children with AT deficiency (95% CI: 3.12-24.42), a high number of mutations (95% CI: 3.43-23.06), or prethrombotic myocarditis (95% CI: 1.61-4.29). [30]
Patients with thrombosis have been encouraged by clinicians to get tested for homocysteine levels and methylenetetrahydrofolate reductase (MTHFR) mutations over the last five or six years. However, Simone et al. discovered that this did not lead to thrombosis. It is recommended that these tests be eliminated from thrombosis panels. [31]

High risk patients for hereditary thrombophilia

Patients with malignancy: Patients with leukemia are at an increased risk of thrombosis because to the use of steroids, L-asparaginase, and catheters. [32]
Neonatal period: Catheters are the most common cause of infant thrombosis, while at least one other factor is present in 95% of cases. Genetic thrombophilia is less prevalent than acquired causes. [12]. Although it is rare, problems in newborns caused by catheter-related thrombosis can be fatal. In addition to the 89% of newborn throm-

bosis cases previously connected to catheters, new study shows that 54% of venous thrombosis cases and 27% of arterial thrombosis cases are associated with catheters. [7] The decrease in catheter-related thrombosis in babies can be attributed to the use of more suited catheters, improved catheter care, and the prevention of clots by the administration of heparin. [9]

Peripheral and umbilical catheters account for 80% of newborn thromboses. The most common locations for this syndrome to occur are in the hepatic vein, right atrial, and inferior vena cava veins. For a more potent treatment, low-molecular-weight heparin and thrombolytic drugs can be used. While prophylactic heparin cannot eliminate the risk of thrombosis, it can prolong the life of a catheter and reduce the probability of occlusion . [33]

The majority of thromboses in newborns do not involve catheters, with renal vein thrombosis (RVT) being the most common type. In about half of these instances, the thrombus moves down the inferior vena cava, and almost 60% of these thrombuses impact both sides of the heart. Neonatal hypoxia, intrauterine growth restriction (IUGR), sepsis, and polycythemia are all variables that increase the risk. It affects 2.2% of the population per 100,000 .[33]

Children with heart disease: Thrombosis is commonly caused by cardiac diseases such cardio-myopathy and congenital heart abnormalities. Additionally, there are other important acquired risk factors including as infection, hypoxia, surgery, angiography, and catheterization. [34]

Children with nephrotic syndrome: Inadequate production of AT and PS can lead to thrombosis in 9-36% of children diagnosed with nephrotic syndrome. [35]

Stroke-transient ischemic attack: Upon diagnosis of transient ischemic attack or neonatal stroke, it is crucial to thoroughly assess the deficiency in AT, PC, and PS. Keep in mind that babies naturally have low amounts of AT, PC, and PS while making your diagnosis. [9]

Juvenile strokes are associated with thrombophilia, similar to venous thromboembolism, in 20-50% of cases. Elevated lipoprotein (a), PC insufficiency, FVL, and PTM are risk factors for stroke recurrence in older children. [36]

Families of children carrying hereditary thrombophilia factor: Thrombophilia testing in youngsters has additional benefits, one of which is the identification of inherited risk factors in those who do not yet exhibit any symptoms. In the presence of a triggering event, thrombosis is more likely to occur in individuals carrying the PC, PS, or AT mutations as compared to those carrying the FVL or PTM mutations. [37]

- **Acquired prothrombotic risk factors:** Acquired thrombotic risk factors include a variety of clinical conditions that may increase the likelihood of vascular thromboembolism. Pediatric thromboembolic stroke risk factors include prescribed medications (such as prednisone, Escherichia coli asparagenase, heparin, antifibrinolytic agents, and contraceptives), complications during pregnancy or delivery, medical procedures, acute illnesses (like sepsis and dehydration), and chronic diseases (like cancer, renal disease, cardiac disease, collagen disease, and rheumatic diseases). [38]

1. Central venous catheters: The use of CVCs has increased in importance and has greatly improved people's quality of life as a medical and supportive therapy tool for many different types of diseases. Major complications include systemic infections, thrombotic occlusion, and deep vein thrombosis (DVT) linked with CVCs. In most cases, CVCs are the main factor that causes a central vein thrombosis (DVT). The reported incidence of CVC-related deep vein thrombosis (DVT) ranges from 1% to over 70%, which is mostly because to the varied definitions, diagnostic techniques, and levels of monitoring that are in use. [39]

2. Childhood cancer: The higher risk of acquiring TE in adult cancer patients is well-documented. With the exception of ALL, our understanding of TE in pediatric cancers is limited. Central venous catheter use is not associated with increased risk of TE in ALL youngsters. Possible causes of TE in cancer include an imbalanced hemostatic system, hypercoagulability, and genetic thrombophilia. Besides the tumor itself, additional possible reasons include therapeutic adverse effects (such as infections or dehydration), central vein thrombosis (CVCs), infectious diseases, and tumors. [40]

3. Acute inflammation/infections: Thrombosis and inflammation are two distinct but interconnected medical issues that, although being physiologically independent, have garnered a great deal of attention in the past decade. Inflammation triggers the activation of the coagulation system, which stops the infection from spreading throughout the body. That aids in preventing the pathogens from penetrating the circulatory system. This reaction is brought on by immunothrombosis, a condition where innate immune cells and platelets collaborate to activate the coagulation system .[41]
Infectious diseases have shaped the human hemostatic system through evolutionary pressures. A streptokinase that preferentially activates human plasminogen was developed by group A streptococcus; this instance exemplifies the pathogen-host arms race in physiological coagulation factor interactions. Microvascular and macrovascular thrombosis, as well as tissue damage, can result from an overactive and unregulated immune and coagulation system in thrombo-inflammation, a disease distinct from healthy immune-thrombosis. The inflammatory and coagulation systems have traditionally been considered distinct, which has limited our capacity to fully understand the hypercoagulability mechanisms described by the Virchow triad. [42]
As is the case with both chronic and acute inflammatory disorders, individuals with COVID-19 are at high risk for thrombosis and coagulation problems. The cytokine storm that COVID-19 patients undergo is a significant pathophysiological relationship between inflammation and thrombosis. [43]

Most cases of SARS-CoV-2 in children are mild and seldom deadly. Nevertheless, there is mounting evidence that SARS-CoV-2 can induce a severe sickness and long-term consequences known as pediatric inflammatory multisystem syndrome (MIS-C linked with COVID-19). [44]. A few weeks after an infection has taken root, MIS-C typically shows up. Shock, organ failure, and death can occur in the worst instances, while symptoms in children can range from persistent inflammation and fever to those observed in a Kawasaki-like sickness .[45]

4. Antiphospholipid syndrome (APS): The antibody-mediated thrombophilia disorder known as APS is characterized by the presence of antiphospholipid antibodies (APA) in the blood together with specific clinical indicators of venous, arterial, or small artery thrombophilia at any site. Acute ischemic stroke (AIS), transient ischemic attack (TIA), and deep vein thrombosis (DVT) are additional symptoms. A number of autoimmune diseases have been associated with APS. [46]
The binding of APA to anionic protein-phospholipid complexes is involved in every conceivable pathophysiological mechanism. This binding activates endothelial cells, platelets, and prothrombin; it also disrupts the binding of annexin V to phospholipids coating the vascular system; and it interferes with fibrinolysis and natural inhibitory pathways. It is possible that diagnostic and therapeutic criteria developed for adults might not always apply to youngsters. Recent articles on gene expression patterns have sought to identify small differences in order to prove the therapeutic significance of different APA. [46]
The most common clinical symptom in children is deep vein thrombosis (DVT), but there is a subset of children who have perinatal stroke and can be treated with secondary antithrombotic prophylaxis without recurrence risk, and there is a high risk of recurrence without adequate long-term anticoagulation. [6]

5. Drugs induced thrombosis

5.1. Heparin-induced thrombocytopenia type 2 (HIT): It is estimated that around 1% of children admitted to pediatric intensive care units have HIT type 2. Following cardiac surgery, the most prevalent causes of venous thrombosis in newborns, infants, and teens treated with unfractionated heparin (UFH) are listed. Patients with HIT are more likely to experience venous TE, while arterial episodes can also occur .[47]

5.2. Glucocorticoids induced thrombosis: Prescriptions for asthma treatment often contain glucocorticoids, which are steroids derived from a precursor that is similar to sex hormones. Therefore, there is scientific evidence to suggest that the use of glucocorticoid may increase the risk of venous thromboembolism (VTE), which includes both PE and DVT. [48]

5.3. Antifibrinolytic drugs: The antifibrinolytic drug tranexamic acid is another option. Although

it reduces bleeding generally, it does increase the risk of thrombosis in certain patients. Menorrhagia, hematuria, some types of surgical procedures, and trauma-related bleeding are some of the conditions for which it is recommended. The risk-benefit analysis works out well when you're dealing with serious bleeding. Because the disease is not as bad and there is no hemodilution, the expected benefits are lower for minor bleeding, and the risk of thromboembolism is higher, the harm-benefit analysis for minor bleeding is different from that of severe bleeding. (49)

6. Perinatal causes: Perinatal stroke is a diverse disorder that can occur from time to time as a result of brain damage that have vascular origins. Strokes like this often occur between the 20th week of gestation and the 28th day following delivery. Perinatal stroke affects one in every 2300–5000 births, making it the leading cause of cerebral palsy. However, the actual frequency of this disorder is difficult to determine because it is likely underdiagnosed. (50)

Anatomical anomalies, genetic predispositions, and maternal and obstetrical variables are the unique risk factors for prenatal strokes, which are different from strokes at other ages. But the pathophysiology remains a mystery to us. (51)

Management of thrombosis

Clinical manifestations: Unintentional TEs happen frequently. The size and location of a thrombus determine how it will be seen clinically. Isolated symptoms or sudden, potentially fatal occurrences might be the way it presents itself. When you see swelling, pain, or cyanosis in your legs, it's likely that you have venous thrombosis. Hepatomegaly and splenomegaly are symptoms of liver failure that may indicate the presence of a thrombus in the portal vein. The symptoms of an upper limb thrombus include chylothorax, chylopericardium, and superior vena cava syndrome. (52)

Swelling, discomfort, and discoloration of the limbs are the acute manifestations of deep vein thrombosis (DVT). Depending on the location and course of the thrombus, signs of vena cava inferior thrombosis might include protruding cutaneous veins and, in rare instances, problems with the kidneys or liver. Symptoms of a thrombosis in the superior vena cava include acute heart failure, cyanosis, and swelling of the neck and upper chest with conspicuous collateral veins. Portal vein thrombosis, which is typically induced by central catheters, and renal vein thrombosis, which is commonly associated with hematuria, can severely damage or even kill the liver and kidneys. (13)

Sudden chest pain and difficulty breathing might be signs of a pleural embolism. Sinus venous thrombosis symptoms may include new headaches, visual problems, seizures, or venous congestion. Central venous catheter (CVC)-associated deep vein thrombosis (DVT) can cause a loss of patency in the CVC, which can lead to the need for local thrombolytic therapy or a replacement of the CVC. It can also cause sepsis if the CVC is involved, or prominent collateral circulation over the chest, neck, and head. (13)

Investigations: Confirmation of thrombophilia requires two tests. The tests should be repeated three to six months after the first diagnosis of acute thrombosis if the patient is not taking an anticoagulant. At this time, confirming a diagnosis of thrombosis cannot be done by any known specialized diagnostic laboratory testing. We cannot use high D-dimer levels to diagnosis juvenile VTE since no clinical trials have shown that this is the case. (53)

Color Doppler ultrasonography, traditional and MRI angiography, lineograms, and echocardiography are some of the diagnostic imaging methods used for occlusion of arteries. While imaging modalities such as echocardiography, CT scans, and MRI can identify pulmonary embolisms in the proximal pulmonary arteries, they are not very good at detecting clots further out from the heart. Ventilation and perfusion scintigraphies are recommended procedures for children in these cases. (6)

Therapy and Prophylaxis: The primary goals of treatment for thrombosis are the prevention of emboli in the lungs and central nervous system, as well as their recurrence and mortality. (54). Prompt and thorough evaluation and therapy are necessary for children with thrombosis because of their long-life expectancy (60-80 years), high risk of recurrence, and good chance of determining the underlying cause. Thrombolytic therapy has a 90% success rate in reopening blocked arteries in

youngsters, whereas anticoagulant medication has a 50% success rate. [9]

Regardless of the underlying cause, the therapeutic objectives for any thromboembolic manifestation should be to completely recanalize the blocked channel and terminate the thrombotic process. Thrombosis is normally cured with heparin therapy, which usually lasts for 5 to 14 days. Patients who are at high risk of organ failure due to extensive thrombosis should not undertake thrombolytic therapy or surgical embolectomy, two more risky therapeutic options. [55]

Commonly used anticoagulants

Unfractionated heparin: There are a number of potential risks associated with aPTT monitoring, including pre-analytical errors, hemorrhage, HIT, the need for venous access for therapy and monitoring, changes in the drug's pharmacokinetics with age, and the need for appropriate AT levels. Intravenous UFH is the sole acceptable method of administration when first beginning antithrombotic medication; LMWH can be used subsequently. [56]

Low-molecular-weight heparin: Advantages include less complications with bleeding and a decreased risk of HIT, as well as predictable pharmacokinetics, little monitoring, and simple once-daily subcutaneous dosing without venous access. Doses required for newborns under 5 kg were almost 50% higher than those needed for older children to achieve the same level of anti-FXa. Our typical advice is LMWH with therapeutic anti-Xa levels for 4-6 weeks, followed by a prophylactic dosage for up to 6 months. [57]

Table (1) Recommended dosing of UFH and LMWH in neonates and children. [13]

UFH i.v.	Neonates < 5kg	Children > 5kg	Target aPTT at 4h
loading dose	1 × 75 U/kg/10 min	1 × 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 × 2.0 mg/kg/d	1 × 1.5 mg/kg/d	0.4–0.8 U/mL
Dalteparin	1 × 200 U/kg/d	1 × 150 U/kg/d	0.4–0.8 U/mL
Reviparin	2 × 150 U/kg/d	2 × 100 U/kg/d	0.5–1.0 U/mL
initial prophylactic dose			
Enoxaparin*	1 × 1.5 mg/kg/d	1 × 1.0 mg/kg/d	< 0.4 U/mL
Dalteparin	1 × 100 U/kg/d	1 × 50 U/kg/d	< 0.4 U/mL
Reviparin	2 × 50 U/kg/d	2 × 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

Thrombolytic agents: When looking for an agency, think about rt-PA. Since streptokinase can induce allergic reactions, it is not recommended for use. If the thrombosis is serious enough to cause organ damage or death, rt-PA may be necessary. Keep in mind that there are the same relative contraindications for children as there are for adults. [58]

Vitamin K antagonists: Vitamin K-dependent protein g-carboxylation can be inhibited by oral anticoagulants such as warfarin and phenprocoumon. Food, co-medication, concurrent illness, and difficult monitoring all contribute to a great deal of variability, therefore careful monitoring and dosage change are required. Vitamin K antagonists should be administered in cases when the prophylaxis lasts more than 6 months. [59]

When treating venous thromboembolism (VTE) in children, heparins, particularly low-molecular-weight and unfractionated heparins, and vitamin K antagonists are utilized. Attack therapy should include heparin for the first 7–10 days, followed by overlapping administration of LMWH or VKAs. [1]. In 2012, the American College of Chest Physicians advised the following therapy for adolescent VTE: anticoagulant medication for three months for induced VTE, six to twelve months for initial unprovoked VTE, and indefinitely for repeated unprovoked VTE. It was last updated by the committee. Longer preventative periods may be beneficial for
children who have a higher risk of inheriting thrombophilia. [1]

Therapeutic relevance is defined as an International Normalized Ratio (INR) between 2.0 and 3.0. Warfarin is usually administered at a dosage of 0.1 to 0.2 mg/kg as a starting point. It is difficult to keep VKAs in infants because of the tablet-only formulation, dietary restrictions, frequent laboratory testing, and greater doses required in newborns. The monitoring should consider intercurrent infections, other medication changes, and diet. [60]

Infusion of deficient inhibitors of hemostasis: For thrombus patients who have coagulation inhibitor deficiencies due to genetics or injury, replacement therapy is an option to consider. An inhibitor shortage can induce purpura fulminans, although there are AT and PC concentrations that are commercially accessible and can save lives in certain circumstances.. [61]

New anticoagulants: Since the limits of traditional anticoagulants are particularly apparent in children, it is crucial to promote the newly permitted drugs for adults. The following medications have only been tested in pediatric patients: the pentasaccharides fondaparinux and idraparinux; the direct thrombin inhibitors hirudin, bivalirudin, and argatroban; and the ximelagatran, which was withdrawn from sale because of liver damage .[62]

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