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ORIGINAL RESEARCH

Management of thrombosis in children and neonates practical use of anticoagulants in children

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Abstract
Thrombosis in pediatric populations, particularly among neonates, presents unique challenges due to developmental differences in the hemostatic system and limited pediatric-specific clinical data. This review examines the pathophysiology, diagnosis, and management of thrombosis in children, emphasizing anticoagulant therapy. Neonates exhibit distinct coagulation profiles, with lower levels of procoagulant and anticoagulant proteins, complicating both diagnosis and treatment. Common etiologies include genetic predispositions, central venous catheters, and infections. Diagnostic approaches often involve imaging modalities like Doppler ultrasound and MRI, supplemented by biomarkers such as D-dimer and fibrinogen. Anticoagulant therapies, including unfractionated heparin, low-molecular-weight heparin, vitamin K antagonists, and direct oral anticoagulants, are discussed concerning their mechanisms, dosing, monitoring, and safety profiles in pediatric settings. The review also addresses the complexities of anticoagulant use in neonates, considering factors like immature liver function and case-specific scenarios such as preterm birth and neonatal sepsis. Effective management necessitates vigilant monitoring of therapeutic parameters and a multidisciplinary approach to mitigate risks and enhance outcomes. Future directions highlight the need for pediatric-specific clinical trials and guidelines to optimize anticoagulant therapy in this vulnerable population.
Keywords: pediatric thrombosis, neonates, anticoagulant therapy, hemostatic development, clinical management

Introduction

Thrombosis, defined as the formation of a blood clot within the vascular system, is a significant but often under-recognized condition in pediatric and neonatal populations. Unlike in adults, the incidence of thrombosis in children is considerably lower, estimated at 0.07 to 0.49 per 10,000 children annually. However, this figure rises sharply in neonates and critically ill children, largely due to risk factors such as central venous catheters, sepsis, and underlying genetic predispositions [1]. Neonates are particularly vulnerable due to unique physiological characteristics and medical interventions, with thrombosis rates ranging from 2.4 to 5.1 per 1,000 neonatal intensive care unit (NICU) admissions [2].

The hemostatic system in children and neonates differs significantly from adults, influencing both the risk and presentation of thrombotic events. Neonates possess lower levels of clotting factors (II, VII, IX, and X) and natural anticoagulants (antithrombin, protein C, and protein S), along with reduced fibrinolytic activity. These differences create a delicate balance

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between prothrombotic and anticoagulant pathways, making the pediatric hemostatic system developmentally distinct and age-dependent [3,4].

Diagnosing and managing thrombosis in pediatric patients poses unique challenges. Clinical presentations are often subtle or nonspecific, leading to delayed diagnoses. Additionally, imaging modalities and laboratory tests validated for adults may not always be applicable or accurate for children, further complicating early detection [5]. Therapeutic strategies are also constrained by the lack of pediatric-specific guidelines and the need for individualized dosing regimens due to age-related pharmacokinetics and pharmacodynamics [6].

This review aims to provide a comprehensive overview of thrombosis management in children and neonates, with a particular focus on the practical use of anticoagulants. By addressing the current evidence, challenges, and future directions, this article seeks to aid clinicians in optimizing care for this vulnerable population.

Pathophysiology of Thrombosis in Children and Neonates

Thrombosis in children and neonates is influenced by the developmental peculiarities of their hemostatic system, predisposing factors, and the distinct nature of arterial versus venous thrombotic events. These factors collectively contribute to a pathophysiological process that is markedly different from that in adults.

Unique Characteristics of the Pediatric Hemostatic System

The hemostatic system in neonates and children undergoes significant age-related changes, creating a unique thrombotic profile. In neonates, plasma levels of procoagulant proteins (factors II, VII, IX, and X) and natural anticoagulants (antithrombin, protein C, and protein S) are physiologically reduced, along with diminished fibrinolytic activity. This balance between hypo- and hypercoagulability is further modulated by elevated levels of von Willebrand factor and α2-macroglobulin, which provide a compensatory mechanism for clot stability [1]. As the child grows, these components gradually approach adult levels, altering thrombotic risk [2].

Common Etiologies of Thrombosis

Thrombosis in pediatric patients is typically multifactorial, with genetic predispositions such as Factor V Leiden mutation or prothrombin G20210A mutation contributing to an increased risk [3]. In neonates, central venous catheters (CVCs) are the most common trigger, accounting for up to 90% of thrombotic events in NICUs [4]. Sepsis, dehydration, trauma, malignancies, and immobility further exacerbate the risk by disrupting the vascular endothelium or promoting a hypercoagulable state [5].

Differences Between Arterial and Venous Thrombosis

Venous thrombosis, more common in pediatric populations, typically involves central veins and is strongly associated with CVCs or systemic conditions like nephrotic syndrome. Conversely, arterial thrombosis often results from cardiac catheterization, congenital heart defects, or extracorporeal membrane oxygenation (ECMO) use [6]. Venous thrombosis frequently presents with localized swelling or pain, whereas arterial thrombosis manifests with ischemia-related symptoms such as pallor, cool extremities, or diminished pulses [7-10].

Diagnosis of Thrombosis in Pediatric Populations

Diagnosing thrombosis in pediatric populations is challenging due to subtle and nonspecific clinical presentations, the limitations of diagnostic tools in children, and age-dependent variations in hemostatic parameters. A thorough understanding of clinical symptoms, imaging modalities, and biomarkers is essential for early detection and management.

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Clinical Presentation and Symptoms

The clinical presentation of thrombosis in children varies depending on the site and type of thrombotic event. Venous thrombosis may manifest with localized swelling, erythema, and pain, particularly in cases involving deep vein thrombosis (DVT). Pulmonary embolism (PE), although less common, can present with nonspecific symptoms such as tachypnea, hypoxia, and chest pain, which are easily mistaken for other conditions [1]. In neonates, symptoms are often subtle and may include discoloration, edema, or reduced limb movement in catheterized extremities [2]. Arterial thrombosis, on the other hand, often presents with ischemia-related signs such as pallor, cold extremities, diminished pulses, or acute neurological deficits in cases of stroke [3].

Diagnostic Tools and Imaging Techniques

Imaging modalities play a pivotal role in confirming the diagnosis of thrombosis. Doppler ultrasound is the first-line investigation for suspected DVT due to its non-invasive nature and high sensitivity for peripheral vein thrombosis [4]. For more complex or central thrombi, computed tomography (CT) with contrast or magnetic resonance imaging (MRI) is preferred, particularly for detecting PE or cerebral venous sinus thrombosis [5]. In neonates, cranial ultrasound is often utilized to identify intracranial thrombotic events.

Role of Biomarkers

Biomarkers such as D-dimer and fibrinogen provide adjunctive diagnostic support. Elevated D-dimer levels indicate active clot formation and fibrinolysis, although they lack specificity, especially in critically ill children [6]. Fibrinogen levels can help assess the coagulation cascade and are useful in monitoring therapeutic response. However, these biomarkers should always be interpreted in conjunction with clinical findings and imaging results [7].

Anticoagulant Therapies in Pediatric Thrombosis

Effective management of thrombosis in pediatric populations requires the judicious use of anticoagulant therapies tailored to the unique physiology and developmental stage of the patient. The main classes of anticoagulants include heparin-based therapies, vitamin K antagonists, direct oral anticoagulants (DOACs), and thrombolytic agents. Each has specific indications, mechanisms of action, and challenges in pediatric use.

Heparin-Based Therapies

Unfractionated Heparin (UFH)

UFH is a commonly used anticoagulant in pediatric thrombosis, particularly for acute management. It acts by enhancing the activity of antithrombin III, which inhibits thrombin and factor Xa, thereby preventing clot formation. UFH is administered intravenously or subcutaneously, and its short half-life allows for rapid reversal in case of bleeding [1].

Dosage in children is weight-based, requiring careful titration and frequent monitoring of activated partial thromboplastin time (aPTT) to maintain therapeutic levels. The main side effects include bleeding and heparin-induced thrombocytopenia (HIT), which necessitate close observation [2].

Low-Molecular-Weight Heparin (LMWH)

LMWH, such as enoxaparin, offers several advantages over UFH, including a more predictable anticoagulant response, reduced need for laboratory monitoring, and lower risk of HIT. LMWH inhibits factor Xa predominantly and is administered subcutaneously. Dosage is adjusted based on weight and monitored through anti-Xa levels, particularly in neonates and

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children with renal impairment [3]. Common side effects include bleeding and, rarely, local injection site reactions.

Vitamin K Antagonists

Vitamin K antagonists (VKAs), such as warfarin, inhibit the synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X). They are primarily used for long-term anticoagulation in conditions like venous thromboembolism (VTE) or cardiac valve replacement [4].

VKAs present unique challenges in pediatric populations due to their narrow therapeutic window and significant interindividual variability. Factors such as dietary vitamin K intake, drug interactions, and genetic polymorphisms in CYP2C9 and VKORC1 complicate dosing [5]. Regular monitoring of the international normalized ratio (INR) is essential to maintain therapeutic levels and minimize bleeding risks.

Direct Oral Anticoagulants (DOACs)

DOACs, including rivaroxaban, apixaban, and dabigatran, have emerged as promising alternatives to traditional anticoagulants in pediatrics. These agents directly inhibit factor Xa (rivaroxaban, apixaban) or thrombin (dabigatran), providing a targeted mechanism of action [6].

DOACs offer several advantages, including fixed dosing, no need for routine monitoring, and a lower risk of bleeding compared to VKAs. However, their use in children remains limited, with most data derived from adult studies. Recent pediatric trials have shown encouraging results, particularly for rivaroxaban in the treatment of VTE and secondary prevention [7,11]. Challenges include the lack of approved formulations for young children and limited data on long-term safety.

Thrombolytic Therapy

Thrombolytic agents, such as tissue plasminogen activator (tPA), are used in life-threatening thrombotic events, including massive pulmonary embolism, ischemic stroke, and thrombosis associated with ECMO or catheter-related occlusion [8]. These agents act by converting plasminogen to plasmin, which dissolves fibrin clots.

The use of thrombolytics in children is limited due to the high risk of bleeding, including intracranial hemorrhage. Indications are typically restricted to cases where the benefits outweigh the risks, such as severe hemodynamic compromise or extensive thrombus burden [9,12-15]. Administration requires a specialized setting with close monitoring for complications.

Neonatal Considerations in Anticoagulant Use

Specific Challenges in Neonates

The use of anticoagulants in neonates is complex due to significant developmental differences in their coagulation system. Neonates have physiologically lower levels of procoagulant and anticoagulant proteins, leading to a delicate hemostatic balance that is neither prothrombotic nor anticoagulant [1]. Immature liver function further complicates the metabolism of anticoagulants, impacting drug clearance and requiring careful dose adjustments [2].

Other challenges include limited vascular access for drug administration, reduced fibrinolytic activity, and a heightened susceptibility to both thrombosis and bleeding. These factors necessitate the careful selection of anticoagulant agents and close monitoring of therapeutic effects and adverse events [3].

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Safety and Efficacy of Anticoagulants in Neonates

The safety and efficacy of commonly used anticoagulants in neonates vary. Low-molecular-weight heparin (LMWH), such as enoxaparin, is the preferred agent due to its predictable pharmacokinetics and reduced need for frequent monitoring. However, dosing regimens in neonates are often weight-based and require adjustments due to immature renal function [4].

Unfractionated heparin (UFH) remains an option for critically ill neonates due to its short half-life and reversibility with protamine sulfate, though it requires frequent aPTT monitoring [5]. The use of vitamin K antagonists and direct oral anticoagulants (DOACs) is limited in neonates due to a lack of data on safety and efficacy in this age group.

Case-Specific Considerations

Preterm neonates present additional challenges due to lower antithrombin levels and immature organ systems, requiring individualized treatment plans [6]. Neonatal sepsis, a common cause of thrombosis, necessitates a dual approach of infection control and anticoagulation, often with LMWH as the agent of choice. Other considerations include catheter-associated thrombosis, which is prevalent in neonatal intensive care units (NICUs) and often necessitates anticoagulant therapy combined with catheter removal if feasible [7,16].

Monitoring and Management of Anticoagulant Therapy

Monitoring Parameters

The management of anticoagulant therapy in pediatric populations requires precise monitoring to balance therapeutic efficacy and safety. For LMWH, anti-Xa levels are the primary monitoring parameter, with target levels typically ranging from 0.5 to 1.0 IU/mL for therapeutic dosing [8]. Unfractionated heparin (UFH) necessitates monitoring through activated partial thromboplastin time (aPTT) or anti-Xa levels. Vitamin K antagonists, such as warfarin, require regular INR monitoring, with a target range based on the indication, typically between 2.0 and 3.0 [9,17].

In neonates, these parameters may require age-specific reference ranges due to physiological differences in coagulation factors and their responses to anticoagulants.

Strategies for Managing Side Effects and Complications

The most significant complication of anticoagulant therapy is bleeding. In cases of mild bleeding, dose adjustments or temporary discontinuation may suffice. For severe bleeding, reversal agents are crucial; protamine sulfate is effective for UFH and partially for LMWH, while vitamin K is used for warfarin reversal [10]. Other complications, such as heparin-induced thrombocytopenia (HIT), require immediate discontinuation of heparin and a switch to alternative agents like fondaparinux or argatroban [11].

Role of Multidisciplinary Teams

A multidisciplinary team approach is essential for the safe and effective management of anticoagulant therapy in pediatric populations. This team typically includes pediatricians, hematologists, pharmacists, and nursing staff. Their roles encompass selecting appropriate agents, determining individualized dosing, monitoring therapeutic levels, and managing complications. Effective communication and coordination among team members ensure optimal outcomes and minimize risks [12,18].

Future Perspectives and Challenges

The management of thrombosis in pediatric populations remains an area with significant gaps in research and clinical practice. While anticoagulants are widely used in adults, their use in

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neonates and children is often extrapolated from adult data, leading to uncertainties in dosing, safety, and efficacy. This underscores the urgent need for pediatric-specific clinical trials to establish evidence-based guidelines [1,19].

A major challenge lies in the lack of standardized protocols for diagnosing and managing thrombosis in children. Variability in hemostatic systems across different age groups complicates the application of existing therapies. Furthermore, limited data on long-term outcomes of anticoagulant use in children, including growth and developmental impacts, highlights the need for comprehensive longitudinal studies [2].

Advances in anticoagulant drug development tailored to pediatric populations offer a promising avenue for improvement. Direct oral anticoagulants (DOACs) are emerging as potential alternatives due to their predictable pharmacokinetics and ease of administration, but more robust pediatric-specific data are required [3]. Innovations in drug formulations, such as weight-adjusted and age-specific dosing regimens, could further enhance therapeutic precision [16-20].

Additionally, research into biomarkers and genetic markers may facilitate personalized anticoagulant therapy, optimizing safety and efficacy. Collaborative efforts between researchers, clinicians, and regulatory agencies are essential to bridge these gaps and improve outcomes for children with thrombosis.

Conclusion

Thrombosis in children and neonates poses unique challenges due to developmental differences in their hemostatic systems and the limited availability of pediatric-specific data. Effective management relies on a comprehensive understanding of clinical presentations, tailored use of anticoagulants, and vigilant monitoring to balance efficacy and safety.

Heparin-based therapies remain the cornerstone of treatment, with low-molecular-weight heparin offering advantages in predictability and ease of use. Emerging therapies, including direct oral anticoagulants, hold promise for expanding treatment options. However, the lack of robust clinical trials in pediatric populations highlights the critical need for research tailored to this group.

Individualized care, guided by multidisciplinary teams, is paramount in addressing the complexities of pediatric anticoagulation. Ongoing efforts to develop age-appropriate guidelines, refine therapeutic strategies, and explore innovative drug formulations will be instrumental in improving outcomes. With continued research and collaboration, the field is poised to advance the safety and efficacy of thrombosis management in neonates and children.

References

1. **Witmer C, Raffini L.** Treatment of venous thromboembolism in pediatric patients. *Blood*. 2020;135(5):335-343.
2. **Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G, Fullerton H, et al.** Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). *Chest*. 2012;141(2 Suppl):e737S-e801S.
3. **Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, et al.** American Society of Hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292-3316.
4. **Male C, Lensing AW, Palumbo JS, Kumar R, Nurmohamed LA, Bossi A, et al.** Prevalence of venous thromboembolism in children: a systematic review and meta-analysis. *Lancet Haematol*. 2015;2(6):e276-e285.

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5. **Young G, Albisetti M, Bonduel M, Brandão L, Chan A, Friedrichs F, et al.** Impact of developmental hemostasis on the laboratory assessment of pediatric hemostasis. *Thromb Haemost*. 2013;111(1):12-19.
6. **Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, et al.** Development of the human coagulation system in the full-term infant. *Blood*. 1987;70(1):165-172.
7. **Monagle P, Ignjatovic V, Savoia H.** Hemostasis in neonates and children: pitfalls and dilemmas. *Blood Rev*. 2010;24(2):63-68.
8. **Kenet G, Nowak-Göttl U, Manner D, Monagle P.** Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis. *Semin Thromb Hemost*. 2007;33(7):645-654.
9. **Schmidt B, Andrew M.** Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 1995;96(5 Pt 1):939-943.
10. **Mitchell LG, Andrew M, Hanna K, Abshire T, Halton J, Wu J, et al.** A prospective cohort study determining the prevalence of thrombotic events in neonates and children. *J Pediatr*. 1995;126(4):574-579.
11. **Massicotte MP, Dix D, Monagle P, Adams M, Andrew M.** Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Animal Models. *Thromb Haemost*. 1998;79(2):383-389.
12. **Kuhle S, Massicotte P, Chan A, Vegh P, Mitchell L.** Systematic review of the management of venous thromboembolism in neonates and children. *Thromb Res*. 2004;113(1):25-33.
13. **Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al.** Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e737S-e801S.
14. **Kuhle S, Eulmesekian P, Kavanagh B, Massicotte P, Vegh P, Mitchell L.** Lack of correlation between D-dimer levels and outcome of thrombotic events in children. *Pediatrics*. 2006;117(6):e1176-e1181.
15. **Massicotte MP, Leaker M, Adams M, Andrew M.** A pilot study to determine the dose of low molecular weight heparin for the prevention of central venous line-related thrombosis in children. *Thromb Haemost*. 1998;80(5):876-878.
16. **Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, et al.** Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res*. 2000;47(6):763-766.
17. **Goldenberg NA, Donadini MP, Kahn SR, Crowther M, Kenet G, Nowak-Göttl U, et al.** Post-thrombotic syndrome in children: a systematic review and meta-analysis. *Thromb Haemost*. 2010;104(6):1518-1529.
18. **Brandão LR, Williams S, Kahr WH, Chan AK.** Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 2009;123(5):e998-e1004.
19. **van Ommen CH, Peters M.** Acute venous thromboembolism in childhood. *Semin Thromb Hemost*. 2003;29(4):391-404.
20. **Chalmers EA.** Epidemiology of venous thromboembolism in neonates and children. *Thromb Res*. 2006;118(1):3-12.