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Review Article

Hemostatic Testing in Critically Ill Infants and Children

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ABSTRACT

Hemostatic testing in critically ill infants and children is essential yet challenging due to the immaturity and dynamic nature of the pediatric hemostatic system. Unlike adults, children, especially neonates, exhibit unique developmental differences in platelet function and coagulation factors, posing challenges for standard reference ranges and inadequate testing protocols, which mislead pediatric patients. Critical illnesses such as sepsis, trauma, liver dysfunction, and hematological or autoimmune disorders often exacerbate these vulnerabilities, increasing the risks of both bleeding and thrombotic complications. A broad spectrum of hemostatic disorders is encountered in this population, including quantitative and qualitative platelet abnormalities as well as inherited and acquired coagulation defects. Diagnostic evaluation relies on a combination of fundamental laboratory tests (platelet count, PT, aPTT, fibrinogen, BT, CT) and advanced assays (such as thromboelastography) to provide a comprehensive assessment. However, the accuracy and reliability of these tests are often compromised by errors, particularly concerning specimen handling and age-appropriate interpretation. Ultimately, healthcare professionals should have a thorough understanding of developmental hemostasis, meticulous adherence to testing protocols, and careful clinical interpretation are crucial for optimizing pediatric outcomes. Ongoing research into pediatric-specific norms and newer global assays will further enhance targeted and effective management strategies.

KEYWORDS

• Thrombocytopenia • Platelet • Clotting factors • Thromboelastography • Hemostasis • Pediatrics • Critical Illness

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INTRODUCTION

Hemostasis, the intricate physiological process that prevents blood loss from injured vessels while maintaining blood fluidity within the vasculature, is critically important for survival. Critically ill infants and children are at high risk for both bleeding and thrombotic complications. Unlike adults, their hemostatic system is immature, with significantly different levels of procoagulant, anticoagulant, and fibrinolytic factors. This physiological difference means that standard adult reference ranges for coagulation tests are often inappropriate and can lead to misinterpretation, potentially resulting in delayed or incorrect management. The complex interplay of underlying critical illness (e.g., sepsis, organ failure, major trauma), therapeutic interventions (e.g., fluid resuscitation, blood product transfusions, mechanical circulatory support), and the inherent immaturity of the hemostatic system make an accurate assessment and timely intervention paramount. The goal of hemostatic testing in this population is to rapidly identify the specific derangement (bleeding tendency or prothrombotic state) and plan individualized therapy.[1,2]

HEMOSTASISPROCESS:DEVELOPMENTAL PERSPECTIVE

Hemostasis is a physiological process that maintains vascular integrity by balancing procoagulant and anticoagulant forces, preventing both excessive bleeding and inappropriate clot formation. It stops bleeding following vascular injury, protecting against blood loss and maintaining circulatory integrity. The process involves several coordinated steps:

Vascular Spasm (Vasoconstriction): Immediately after blood vessel injury, it constricts to reduce blood flow and limit blood loss. This is mediated by factors such as endothelin released from damaged endothelium.

Primary Hemostasis (Platelet Plug Formation): Platelets adhere to exposed subendothelial collagen and von Willebrand factor at the injury site, become activated, and aggregate to form a platelet plug. This plug provides an initial barrier to bleeding.

Secondary Hemostasis (Coagulation): A complex cascade of enzymatic reactions activates clotting factors, leading to the conversion of fibrinogen to fibrin by thrombin. Fibrin strands reinforce and stabilize the platelet plug, forming a robust blood clot.

Clot Retraction and Fibrinolysis: After the vessel is repaired, the clot is gradually dissolved by the fibrinolytic system, primarily through the action of plasmin, to restore normal blood flow and prevent excessive clotting.[3]

DEVELOPMENTAL HEMOSTASIS

The hemostatic system undergoes significant maturation from fetal life to adulthood. Neonates, especially premature infants, have quantitatively lower levels of most vitamin K-dependent factors (Factors II, VII, IX, X), contact factors (Factors XI, XII), and natural anticoagulants (Antithrombin, Protein C, Protein S) compared to adults. Conversely, they may have relatively higher levels of von Willebrand factor (vWF) and Factor VIII, and a distinct "fetal fibrinogen" with altered polymerization properties. This unique profile means that while healthy neonates are generally "physiologically hypocoagulable" compared to adults, their system is inherently balanced. However, this balance is easily disrupted by critical illness, leading to a narrow margin for error and a propensity for severe bleeding or thrombosis. The reference ranges for coagulation tests are therefore highly age-dependent, gradually normalizing to adult values over the first 6-12 months of life, and at most values reach adult norms.[4]

DISORDERS OF HEMOSTASIS

Critically ill pediatric patients are susceptible to a wide range of hemostatic disorders, leading to either bleeding or thrombotic complications. These disorders are often multifactorial and can be exacerbated by the underlying critical illness.

Platelet disorders in pediatrics can be broadly categorized into quantitative issues, affecting platelet count, and qualitative issues, affecting platelet function (thrombocytopathies). Disorders of platelet count include Thrombocytopenia (Low Platelet Count), a common cause of bleeding, with examples like Immune Thrombocytopenia (ITP) and Neonatal Alloimmune Thrombocytopenia (NAIT). Conversely, Thrombocytosis (High Platelet Count) can also occur. Regarding

platelet function, Disorders of Platelet Function (Thrombocytopathies) are either Inherited Platelet Function Disorders, such as Glanzmann Thrombasthenia, Bernard-Soulier Syndrome, and Storage Pool Deficiency, or Acquired Platelet Dysfunction, often Medication-Induced, or resulting from underlying conditions like Uremia (Kidney Failure) and Liver Disease.[5]

Coagulation disorders, which are a type of bleeding disorder, can be either inherited or acquired in pediatric patients. Inherited Coagulation Factor Deficiencies include well-known conditions such as Hemophilia A (Factor VIII Deficiency), Hemophilia B (Factor IX Deficiency), and Von Willebrand Disease (VWD). In addition to these genetic predispositions, several Acquired Coagulation Disorders can arise, including Vitamin K Deficiency Bleeding (VKDB), severe Liver Disease / Liver Failure, Disseminated Intravascular Coagulation (DIC), coagulopathy due to Massive Transfusion, and rare cases of Acquired Hemophilia.[6]

Clotting, or thrombotic, disorders can be broadly categorized into inherited and acquired conditions. Inherited Thrombophilias represent genetic predispositions to clot formation and include common mutations like Factor V Leiden and Prothrombin G20210A, as well as deficiencies in natural anticoagulants such as Antithrombin Deficiency, Protein C Deficiency, and Protein S Deficiency. More frequently, Acquired Thrombotic Disorders are encountered, with Central Venous Catheters (CVCs) being a predominant risk factor. Other significant acquired causes include systemic conditions like Sepsis/Severe Infection, states promoting blood stasis or viscosity such as Dehydration/Polycythemia and Immobility/ Prolonged Bed Rest, and underlying medical conditions like Congenital Heart Disease, Malignancy (e.g., Acute lymphatic leukemia-ALL), and Nephrotic Syndrome. Additionally, exposure to Mechanical Circulatory Support, certain Medications like anticoagulants (Blood thinners), and events like Perinatal Asphyxia can contribute to the development of thrombotic disorders in children.[7]

HEMOSTATIC TESTING METHODS

Hemostatic testing in critically ill children and infants presents unique challenges due to the dynamic nature of their developing hemostatic system. The array of tests available, from routine screening panels to specialized global assays, provides crucial insights into a child's bleeding risk or thrombotic predisposition, guiding targeted interventions that can be life-saving in the fast-paced critical care environment. The diagnostic approach in critically ill children often starts with routine screening tests, followed by more specialized assays based on clinical suspicion. Understanding what each test measures, its age-appropriate values, and its clinical significance is vital for any clinician managing these vulnerable patients. Given these nuances, a range of laboratory tests, both traditional and newer "global" assays, are employed to provide a comprehensive assessment of the hemostatic system in critically ill pediatric patients, as described in Table 1.

Table 1: Assessment of Hemostatic Parameters in Critically Ill Pediatric Patients

Hemostatic Test	Approximate Age-Specific Values	Indications	Clinical Significance
		Traditional Hemostatic Tests	
Platelet Count (PLT)[8,9]	**Neonates (Term):** 250,000 to 450,000/mL **Infants/Children:** 150,000 to450,000/mL (similar to adults)	**Bleeding:** Overt bleeding (epistaxis, GI bleed, intracranial hemorrhage), excessive bruising/ petechiae. **Critical Illness:** Sepsis, DIC, multi-organ dysfunction, major trauma, liver failure, post-ECMO. **Monitoring:** Chemotherapy, bone marrow suppression.	**Low (Thrombocytopenia):** Increased risk of bleeding (severity proportional to platelet drop). Indicates consumption, destruction, or decreased production and infections like Dengue, malaria, sepsis, and snake bite. **High (Thrombocytosis):** Often reactive (inflammation, infection); rarely, primary myeloproliferative disorders.
Bleeding Time (BT)[10]	**Neonates:** 2-9 minutes **Infants/Children:** 2-7 minutes	Screening for primary hemostasis disorders (platelet function, vWD).	**Prolonged BT:** Suggests impaired platelet function, thrombocytopenia, or von Willebrand disease and infections like Dengue, malaria, sepsis.

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Hemostatic Test	Approximate Age-Specific Values	Indications	Clinical Significance
		Traditional Hemostatic Tests	
Clotting Time (CT)[11]	**Neonates:** 5-15 minutes **Infants/Children:** 4-10 minutes	Global assessment of coagulation, monitoring high-dose heparin.	**Prolonged CT:** Indicates severe deficiency of multiple coagulation factors (Hemophilia), severe hypofibrinogenemia, Liver Failure , DIC or presence of strong anticoagulants (e.g., high-dose heparin)
Prothrombin Time (PT)/ INR[12]	**Neonates (Term, Day 1):** 13.0 - 17.0 seconds (INR often 1.0-1.6) **Infants (1-6 months):** May be slightly prolonged, gradually normalizing. **Children (>6 months -Adult):** 10-13seconds (INR generally <1.2)	**Bleeding:** Suspected coagulation factor deficiency, unexplained bleeding. **Critical Illness:** Sepsis, liver dysfunction/failure, DIC. **Monitoring:** Warfarin therapy, Vitamin K status. **Pre-operative assessment.**	**Prolonged PT/Elevated INR:** Deficiency/ dysfunction of extrinsic (Factor VII) or common pathway (Factors II, V, X, Fibrinogen). Indicates impaired vitamin K-dependent factor synthesis, liver dysfunction, or consumption, DIC. Guides FFP/Vitamin K/factor replacement and common pathway factor deficiencies (II, V, X).
Activated Partial Thromboplastin Time (aPTT)[13]	**Neonates (Term, Day 1):** 40-60 seconds (can be longer in preterm infants) **Infants (1-6 months):** Gradually shortens, often normalizing by 6 months to 1 year. Children (>6 months - Adult): 25-35 seconds	Bleeding: Suspected inherited bleeding disorders (e.g., hemophilia, VWD), unexplained bleeding. Critical Illness: Sepsis, DIC, liver disease, congenital heart disease. Monitoring: Heparin therapy (unfractionated heparin).	**Prolonged aPTT:** Deficiency/dysfunction of intrinsic (Factors VIII, IX, XI, XII) or common pathway factors. Indicates inherited coagulopathies, heparin effect, or consumption, Liver Disease, Lupus Anticoagulant. Helps differentiate bleeding causes and guides specific factor replacement /anticoagulation and infections like **Dengue, malaria, sepsis**
Fibrinogen Level[14]	**Neonates (Term):** 1.5 - 4.0 g/L (some sources suggest slightly lower normal range) **Infants/Children:** 1.5 - 4.0 g/L	**Bleeding:** Suspected DIC, massive hemorrhage, liver failure, poor clot formation. **Critical Illness:** Sepsis, trauma, burns.	**Low (Hypofibrinogenemia, <1.5 g/L):** Significant bleeding risk due to impaired clot strength. Indicates consumption (DIC), impaired synthesis (liver disease), or dilution. **High (Hyperfibrinogenemia):** Acute phase reactant, common in inflammation/infection; can contribute to thrombotic risk.
D-dimer[15]	**Neonates:** Physiologically elevated (e.g., up to 0.7-1.0 µg/ mL FEU or higher) due to ongoing physiological fibrin turnover. **Infants/Children (after neonatal period):** Generally <0.5 µg/mL FEU	**Suspected Thrombosis:** Deep vein thrombosis (DVT), pulmonary embolism (PE), catheter-related thrombosis. **Suspected DIC:** In critically ill children with sepsis, malignancy, trauma. **Monitoring:** Fibrinolytic activity.	**Elevated D-dimer:** Indicates ongoing fibrin formation and breakdown. Very high/rapidly rising levels, especially with other coagulopathies, are highly suggestive of DIC. Useful marker for venous thromboembolism (VTE) evaluation. PE, catheter-related thrombosis, Sepsis, Trauma, Major Surgery, Liver Disease, Acute Lymphoblastic Leukemia (ALL).
Thrombin Time (TT)[16]	**Neonates:** 19-30 seconds (can be prolonged due to "fetal fibrinogen") **Infants/Children/Adults: <21** seconds (or lab-specific normal range)	Suspected Heparin Contamination: When PT/aPTT are unexpectedly prolonged. Suspected Fibrinogen Disorder: Dysfibrinogenemia, Hypofibrinogenemia.	Prolonged TT: Problem with the conversion of fibrinogen to fibrin. Suggests Dysfibrinogenemia, Afibrinogenemia, Hypofibrinogenemia, Heparin Contamination/ Overdose.
Factor Assays (e.g., Factor VIII, IX, XIII, vWF Antigen/ Activity)[17]	Highly variable by factor and age. Levels are generally lower in neonates and young infants compared to adults (e.g., Factor VII, IX, X, XI, XII are ~30-60% of adult levels at birth, Factor VIII and vWF may be higher).	**- Diagnosis of specific inherited bleeding disorders**: Following abnormal PT/aPTT or strong clinical suspicion. **- Monitoring therapy** for known deficiencies. **- Evaluation of unresponsive coagulopathy.**	**Low Factor Activity:** Confirms specific factor deficiency. Guides precise replacement therapy. **High Levels (vWF):** Common in neonates, may contribute to prothrombotic tendency.

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Latest Hemostatic Tests			
Visco-elastic Hemostatic Assays (VHEAs: TEG/ROTEM)[18]	Complex parameters (R-time/CT, K-time/CFT, Alpha Angle, MA/MCF, LY30/CL). Age-dependent reference ranges vary by instrument/methodology.	**Major Bleeding:** Trauma, surgery (cardiac, liver transplant), ECMO. **Critical Illness:** Sepsis, liver failure, coagulopathy of critical illness. **Guiding Transfusion:** Targeted blood product administration. **Monitoring Anticoagulation/ Procoagulant Therapy.**	Provides real-time information on clot initiation, formation kinetics, clot strength, and fibrinolysis. Can rapidly identify specific deficiencies (factor, platelet, fibrinogen) or hyperfibrinolysis, allowing for targeted component therapy. Indicates DIC (global hypocoagulability, hyperfibrinolysis), Trauma-induced coagulopathy, Liver disease coagulopathy, Primary hyperfibrinolysis, Platelet dysfunction, Specific factor deficiencies (e.g., severe hemophilia).
Platelet Function Tests (PFA-100/200, Verify Now, Light Transmission Aggregometry)[19]	**PFA-100/200-** Age-specific ranges vary. Generally, longer than adult values in neonates, then shorten. Aggregometry: Varies by agonist and age.	**Unexplained Bleeding:** With normal platelet count and normal PT/aPTT. **Suspected Inherited Platelet Disorder. Monitoring Antiplatelet Therapy** (e.g., aspirin, clopidogrel). **- Renal/Liver Disease:** To assess acquired platelet dysfunction.	**Abnormal Results:** Indicate impaired platelet adhesion, activation, or aggregation. Helps identify qualitative platelet defects. Useful for assessing medication effect on platelets. Inherited platelet function disorders (e.g., Glanzmann Thrombasthenia, Bernard-Soulier Syndrome, Storage Pool Deficiencies), Acquired platelet dysfunction (e.g., uremia, liver disease, medication-induced), Von Willebrand Disease (screening test).

(**Abbreviation: DIC** - Disseminated intravascular coagulation, **ECMO** - Extracorporeal membrane oxygenation, **vWF** - Von Willebrand factor, **TEG** - Thromboelastography, **ROTEM** - Rotational thromboelastography)

Note: Reference ranges given for hemostatic tests, particularly those for pediatric patients, can differ significantly depending on the laboratory protocols, analyzer technology, reagents, methodology, calibration procedures & population differences used. The values provided here are approximate and should always be correlated with the specific validated reference intervals. For clinical decision making, it is essential to interpret results by referring to laboratory-specific, age-adjusted standards and universal cutoffs.

ERRORS IN HEMOSTATIC TESTING

Errors in hemostatic testing can lead to misdiagnosis and inappropriate treatment, particularly in critical care settings. These errors are typically categorized as pre-analytical, analytical, and post-analytical.

Pre-Analytical Errors in Hemostatic Testing

Pre-analytical errors constitute the most common and significant source of inaccuracy in hemostatic (coagulation) testing. These errors occur before laboratory analysis and can profoundly impact test results, sometimes leading to inappropriate clinical decisions. Main Types of Pre-Analytical Errors include.[20-22]

Patient Preparation: Inadequate fasting, strenuous exercise, or use of medications that affect coagulation, such as anticoagulants or NSAIDs, can significantly alter coagulation test results and should be avoided before testing.

Misidentification of patient or sample: Labeling mistakes can result in catastrophic errors in diagnosis and management.

Incorrect blood draw technique: Using the wrong order of draw or improper equipment, applying the tourniquet for too long (which increases tissue factor release and can cause falsely abnormal coagulation results), and performing a difficult or traumatic venipuncture (which may result in local tissue release of clotting factors or hemolysis) are all significant pre-analytical errors that can compromise the accuracy of hemostatic testing

Improper filling of collection tubes: Under- or over-filling of sodium citrate tubes (blue colour) alters the blood-to-anticoagulant ratio, potentially leading to inaccurate results such as falsely prolonged clotting times, particularly in PT/INR and aPTT tests.

Inadequate mixing after collection: Failure to properly invert tubes may result in microclots. Excessive shaking can cause hemolysis and artifactual activation of clotting pathways.

Sample Handling and Transport: Delays in processing, exposure to temperature extremes, or inappropriate storage and agitation can lead to degradation or activation of coagulation factors, resulting in unreliable test results.

Patient-Related Factors: Extremely high hematocrit (e.g., polycythemia) without

adjustment of anticoagulant volume can falsely alter results due to excess citrate.

Analytical & Post-Analytical Errors in Hemostatic Testing

- While less frequent due to modern automation, analytical errors can still occur in hemostatic testing, stemming from issues such as instrument malfunction, problems with reagents, calibration errors, or inadequate quality control. Beyond the laboratory analysis itself, post-analytical errors also pose a risk. These include incorrect reporting of results, transcription errors, and, critically, misinterpretation of the data by clinicians, especially when they fail to account for the unique aspects of developmental hemostasis in children. Mitigating these errors requires meticulous attention to detail during sample collection, adherence to strict laboratory protocols, and continuous education for clinicians on age-specific interpretation.[23-25]

ROLE OF HEALTHCARE PROFESSIONALS IN REDUCING ERRORS

Healthcare professionals, including nurses, Lab technicians, and allied health workers, are crucial in minimizing errors in hemostatic testing by focusing on three key phases: pre-analytical, analytical, and post-analytical. Errors, particularly those in the pre-analytical phase, can significantly impact patient safety and clinical outcomes.

Nurses and Allied Health (Pre-Analytical Phase)

Allied health professionals, such as nurses and phlebotomists, play a vital role in preventing errors during the pre-analytical phase (steps before a sample reaches the lab). This phase is where the majority of errors occur.[26,27]

Patient and Specimen Identification: They must correctly identify the patient using at least two identifiers (e.g., name and date of birth) and label the specimen tubes accurately with the patient's hospital identification number/ bed number. Misidentification can have life-threatening consequences.

Sample Collection: They must follow strict protocols for blood collection, including the correct order of draw and using the right tube with the proper anticoagulant (e.g., 3.2% sodium citrate for coagulation tests). An incorrect blood-to-anticoagulant ratio can lead to inaccurate test results.

Sample Integrity: They need to use proper technique to prevent hemolysis (rupture of red blood cells), which can interfere with test results, and to ensure the sample doesn't clot before it reaches the lab. This includes gentle mixing and avoiding turbulent blood flow during collection.

Timely Transport: They are responsible for ensuring samples are transported to the laboratory promptly and under the correct conditions, as delays can compromise the sample's integrity and alter results.

LAB TECHNICIANS (ANALYTICAL & POST-ANALYTICAL PHASES)

Lab technicians are primarily responsible for minimizing errors in the analytical phase (the testing process) and the post-analytical phase (reporting and interpreting results).[28,29]

Quality Control (QC) & Quality Assurance (QA): Lab technicians run internal and external quality controls to verify the accuracy and precision of instruments, reagents, and test methods. They should use specific rules and charts (e.g., Westgard rules, Levey-Jennings charts) to monitor performance and detect any shifts or trends that could indicate a problem with the analyzer.

Specimen Processing: Ensure that samples are centrifuged and processed correctly to obtain platelet-poor plasma, which is essential for accurate hemostatic testing. Also check for signs of hemolysis, lipemia, or icterus, which can interfere with the optical analysis performed by many modern instruments.

Instrument Maintenance: Perform routine calibration and maintenance on hemostasis analyzers to ensure they are functioning optimally.

Result Verification and Reporting: Review and validate test results, comparing them to previous patient results and flagging any that are inconsistent with the patient's clinical picture. Responsible for accurate and timely reporting of results to clinicians.

CONCLUSION

Hemostatic testing in critically ill children and infants is a cornerstone of diagnosis and management, yet it presents inherent complexities due to developmental hemostasis. A deep understanding of the physiological differences in coagulation parameters across various pediatric age groups is paramount for accurate interpretation. Through meticulous patient and specimen identification, strict adherence to blood collection and processing protocols, consistent quality control, and ongoing education, professionals can help ensure that laboratory results are crucial for optimizing care and improving outcomes. The integral role of healthcare professionals, including nurses, lab technicians, and allied health staff as a multidisciplinary team, is foundational for safe and effective hemostatic testing in critically ill infants and children. Still, they all need sustained education to further empower them to deliver individualized, evidence-based care and ultimately, to improve outcomes for vulnerable pediatric patients.

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