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DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF HEMATOLOGICAL SYNDROMES MANIFESTING COAGULOPATHY AND HEMOLYSIS: A REVIEW CENTERED ON HEMOPHILIA AND SICKLE CELL DISEASE

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ABSTRACT

The greatest challenge in blood health is distinguishing between conditions defined by uncontrolled, dangerous bleeding (like inherited coagulopathies, exemplified by Hemophilia A and B, or HA/HB) and those marked by chronic cell destruction and dangerous clotting (such as Sickle Cell Disease, or SCA). However, the most life-threatening scenarios involve acquired syndromes that manifest a disturbing overlap, where patients suffer both massive bleeding and widespread clotting, including Disseminated Intravascular Coagulation (DIC), Thrombotic Microangiopathies (TTP/HUS), and Paroxysmal Nocturnal Hemoglobinuria (PNH). Accurate and immediate diagnosis demands the use of highly specific tools—from Factor Assays for congenital defects to measuring ADAMTS13 activity for TMA, and advanced flow cytometry for PNH clones. Getting the diagnosis right is the absolute foundation for effective, life-saving management, which ranges from simple Factor replacement to urgent plasma exchange (PEX) and targeted complement inhibition.

INTRODUCTION

1.1 Bleeding or Clotting? The Crisis of Hemostasis

The health of the blood is a constant struggle for balance. Hematological disorders typically break this balance, leaning heavily toward either a state of easy bleeding (hypocoagulable) or excessive clotting and cell breakdown (hypercoagulable/hemolytic). The complexity arises when acute, acquired syndromes, particularly DIC and TTP, exhibit a chaotic mix, blurring the clinical lines between these two extremes. The foundation of effective care is pinpointing the root molecular fault—is it a simple missing clotting factor, an abnormally shaped blood cell, or an acquired disorder of immune or coagulation control?

1.2 Defining the Core Conditions

1.2.1 Hemophilia A and B (HA/HB): A Leaky Faucet

Hemophilia A (Factor VIII deficiency) and Hemophilia B (Factor IX deficiency) are X-linked recessive disorders, meaning they affect males almost exclusively. The core problem is a failure in the **coagulation cascade**, the complex internal mechanism responsible for forming a strong, secondary clot due to insufficient factor activity.

The defining feature of severe hemophilia (factor activity levels below 1%) is deep, spontaneous bleeding, primarily into joints (hemarthroses) and muscles. This deep tissue bleeding can lead to joint crippling and, in severe cases, be life-threatening. Intracranial bleeding is the leading cause of death, while deep muscle bleeds, like those in the iliopsoas, can cause massive blood loss (hypovolemic shock) or airway compromise.

1.2.2 Sickle Cell Disease (SCA): Sticky, Stiff Cells Causing Traffic Jams

SCA is an inherited hemoglobinopathy caused by a single genetic mutation that results in abnormal hemoglobin S (HbS). When deprived of oxygen, HbS molecules stack up and deform the Red Blood Cells (RBCs) into stiff, C-shaped "sickle" cells. This creates two fundamental problems: chronic red cell destruction (hemolysis) and widespread obstruction of small blood vessels (vaso-occlusion). SCA is fundamentally a disorder of both cell destruction and pathological clotting, contrasting sharply with the isolated bleeding problem of classic Hemophilia.

The consequences stem from these processes. Chronic hemolysis causes severe anemia, indicated by low hematocrit and high markers of cell breakdown (LDH, bilirubin). Vaso-occlusion leads to recurrent pain crises (VECs), organ damage (stroke, acute chest syndrome), and chronic inflammation. The destruction of cells releases free hemoglobin, which damages the blood vessel lining (endothelium) and creates a persistent thrombophilic (clotting-prone) status.

Classification

The differential diagnosis must include other inherited mimics, but critically, it must resolve the status of acquired syndromes that actively combine the features of both clotting failure and cell destruction.

2.1 Group I: Inherited Bleeding Disorders (Mimicking Hemophilia)

- **Von Willebrand Disease (VWD):** The most common inherited bleeding disorder. Severe VWD can look clinically similar to Hemophilia A because it also involves severely reduced Factor VIII levels.
- **Other Factor Deficiencies:** Specific lab tests are necessary to exclude rare deficiencies of other coagulation factors (e.g., F VII, X, XI, etc.).

2.2 Group II: Inherited Hemolytic Disorders (Mimicking SCA)

- **Thalassemia Syndromes:** These disorders involve reduced or absent production of globin chains. They are distinguishable from SCA by causing **microcytic** anemia (small cells), but they share the feature of chronic hypercoagulability, especially in Beta-Thalassemia Intermedia.
- **Hereditary Hemolytic Anemias:** Conditions like G6PD deficiency, Pyruvate Kinase deficiency, Hereditary Spherocytosis, and Hereditary Elliptocytosis involve defects in the red cell structure or enzymes. They cause hemolysis but typically lack the severe vascular injury and thrombotic component that defines SCA.

2.3 The Emergency Zone: Acquired Syndromes That Do Both (MAHA/TMA)

These are acute, life-threatening syndromes where patients simultaneously consume clotting factors (causing bleeding risk) and destroy red cells (causing hemolysis). The defining clue is **Microangiopathic Hemolytic Anemia (MAHA)**, characterized by fragmented red blood cells (schistocytes).

- **Disseminated Intravascular Coagulation (DIC):** DIC is uncontrolled, widespread internal chaos. The coagulation system is globally activated, leading to two parallel, deadly effects: microvascular thrombosis (clotting) that causes organ failure, and consumption of all platelets and factors (bleeding). DIC is typically triggered by severe underlying issues like sepsis, massive trauma, or certain cancers. The resulting clots are primarily made of fibrin.
- **Thrombotic Microangiopathies (TMA):** This is a subgroup of MAHA defined by MAHA, severe shortage of platelets (thrombocytopenia), and microvascular thrombosis.
    - **Thrombotic Thrombocytopenic Purpura (TTP):** TTP involves a severe shortage of the ADAMTS13 enzyme (activity <10\%). Without this "cutter" enzyme, ultra-large von Willebrand factor (VWF) proteins accumulate, causing spontaneous platelet clumping and clot formation. TTP clots are distinctively VWF-rich.

- ○ **Hemolytic Uremic Syndrome (HUS):** This is often linked to Shiga toxin-producing bacteria or, in the atypical form (aHUS), to genetic problems with complement system regulation.
- **Paroxysmal Nocturnal Hemoglobinuria (PNH):** PNH is an acquired, rare clonal disorder where a stem cell mutation (*PIGA* gene) causes blood cells to lack crucial surface inhibitors (CD55 and CD59). This leaves the cells vulnerable to uncontrolled complement attack, leading to chronic hemolysis (like SCA) and a very high risk of major thrombosis (like TMA complications). PNH often develops in patients with prior bone marrow failure syndromes (Aplastic Anemia or MDS).

Causes and Risk Factors

3.1 Genetic Etiologies (Inherited)

- **Hemophilia A/B:** X-linked recessive mutations in the F8 and F9 genes.
- **SCA:** Autosomal recessive inheritance of the HbS mutation.
- **Thalassemia:** Autosomal recessive disorders affecting globin chain synthesis.
- **Congenital TMA:** Rare congenital forms of TTP (Upshaw-Schulman syndrome) caused by autosomal mutations in ADAMTS13.

3.2 Acquired Etiologies (Triggers for DIC, TTP, PNH)

- **DIC:** Most cases are triggered by severe illnesses, particularly sepsis (Gram-negative), severe trauma (burns, head injury), obstetric complications (amniotic fluid embolism, retained dead fetus), and specific malignancies (acute promyelocytic leukemia). The prognosis in DIC is heavily influenced by the severity of this underlying trigger.
- **Acquired TTP (Autoantibodies):** Caused by autoantibodies against ADAMTS13. Triggers include autoimmune disorders (like Systemic Lupus Erythematosus), HIV, pregnancy, and certain medications (antiplatelet, anti-arrhythmic drugs).
- **PNH (Somatic Mutation):** This is an acquired disease, not inherited. It requires a somatic mutation in the *PIGA* gene within a hematopoietic stem cell lineage. The PNH clone often expands because the body's misguided immune system destroys the healthy stem cells, allowing the defective PNH stem cells to survive and take over, particularly in the context of Aplastic Anemia or Myelodysplastic Syndrome.

Diagnostic Techniques

Diagnosis moves quickly from general screening to specialized, targeted tests for the suspected molecular fault.

4.1 Initial Screening and Core Assays

- **Coagulation Tests:** The **APTT** (Activated Partial Thromboplastin Time) is prolonged in Hemophilia A/B because it tests Factors VIII and IX. The **PT** (Prothrombin Time) is typically normal in Hemophilia. Overt DIC prolongs **both** PT and APTT due to widespread factor consumption. TMAs (TTP/HUS) typically show normal coagulation screens.
- **Anemia and Hemolysis: MCV** (Mean Corpuscular Volume) distinguishes microcytic anemias (Thalassemia, iron deficiency) from the normocytic anemia of SCA or PNH. Hemolysis is confirmed by high **LDH** and bilirubin.
- **The Smoking Gun (MAHA):** Finding **schistocytes** (RBC fragments) on a blood smear is proof of MAHA, immediately directing the workup toward DIC or TMA. The **DAT** (Direct Antiglobulin Test or Coombs test) is essential; a negative result helps exclude Autoimmune Hemolytic Anemia (AIHA), which is confirmed by a positive DAT, in favor of the mechanical destruction seen in TTP or DIC.

4.2 Specific Diagnostic Assays for Index Disorders

- **Hemophilia:** Specific **Factor Assays** precisely measure the activity of F VIII and F IX to confirm the type and severity.
- **SCA/Thalassemia: Hemoglobin Electrophoresis** identifies the abnormal HbS and other globin chain defects.
- **VWD:** Requires quantitative testing for VWF antigen level, VWF functional activity (RCo), and Factor VIII activity.

4.3 Resolving the MAHA Emergency (TMA, DIC, PNH)

1. **TTP vs. DIC:**

○ **ADAMTS13 Activity:** Severe deficiency, specifically <10\%, is the hallmark of TTP. Critically, the plasma sample must be collected **before** starting Plasma Exchange (PEX) to avoid a false-negative result.

○ **Coagulation Profile:** DIC shows thrombocytopenia, prolonged PT/APTT, low fibrinogen (often <1 g/L), and markedly high D-dimer. TTP typically has a normal coagulation screen (PT/APTT) and preserved fibrinogen levels, contrasting sharply with the global consumption seen in DIC.

2. **Paroxysmal Nocturnal Hemoglobinuria (PNH):** PNH is confirmed by highly sensitive **flow cytometry** to detect the absence of the GPI-anchored proteins (CD55 and CD59) on peripheral blood cells.

Modeling and Analysis

Scoring systems and objective data analysis are vital for rapid, high-stakes decisions in hematologic emergencies.

5.1 Comparative Analysis of Laboratory Profiles (Example Table)

The following table provides a rigorous side-by-side comparison of the laboratory profiles used to differentiate these syndromes:

Table I: Initial Laboratory Differentiation of Core Hematological Syndromes.

Parameter	Hemophilia A/B (Severe)	Sickle Cell Anemia (SCA)	DIC (Overt)	Acquired TTP	PNH (Non-acute)
Primary Pathophysiology	Factor Deficiency (VIII/IX)	HbS Polymerization/ Vaso-Occlusion	Global Coagulation Activation/Consumption	Severe ADAMTS13 Deficiency	Complement-mediated Hemolysis
APTT	Prolonged	Normal	Prolonged	Normal to slightly prolonged	Normal
PT/INR	Normal	Normal	Prolonged	Normal	Normal
Platelet Count	Normal	Normal to Elevated	Low (<50 k/\muL)	Severely Low (Consumption)	Low (If associated BMF)
Fibrinogen	Normal	Normal	Low (<1 g/L)	Normal to High	Normal to High
D-dimer/FDP	Normal	Variable (Often Elevated)	Markedly High (Strong Increase)	Elevated (Moderate)	Elevated (Due to Thrombosis Risk)
Schistocytes (MAHA)	Absent	Mild/Variable	Prominent	Prominent	Absent
ADAMTS13 Activity	Normal	Normal	Normal to Moderate Reduction	<10\% (Diagnostic)	Normal
Reticulocyte Count	Normal	High (Compensatory)	Variable	High (Compensatory)	High (Compensatory)
Diagnostic Confirmation	Factor Assay	Hemoglobin Electrophoresis	ISTH Score \ge 5	ADAMTS13 Assay	Flow Cytometry

5.2 Application of Clinical Scoring Systems (Models Used, Analysis Procedure)

- **ISTH DIC Scoring System:** Used to confirm overt DIC in patients with underlying risk factors (like sepsis). This score integrates quantitative laboratory testing—specifically platelet count, D-dimer, fibrinogen, and PT elongation. A score of \ge 5 is compatible with overt DIC, and monitoring the score is vital as high values correlate with increased mortality.

- **PLASMIC Score:** Acute TTP is often fatal without rapid treatment. The PLASMIC score is a critical bedside tool used to predict the likelihood of severe ADAMTS13 deficiency (<10\%). This risk stratification guides the urgent, empirical initiation of Plasma Exchange (PEX) while awaiting definitive ADAMTS13 results.
- **Advanced Predictive Modeling:** Current research explores integrating extensive clinical parameters, including cytokines and cell population data, into machine learning models to improve the classification and differential diagnosis of complex hematological diseases, sometimes achieving diagnostic accuracy comparable to or better than experienced hematologists.

RESULTS AND DISCUSSION

6.1 The Rare Paradox: Living with Both Hemophilia and Sickle Cell Disease

The simultaneous inheritance of severe Hemophilia (a bleeding disorder) and a thrombophilic hemoglobinopathy (SCA or Sickle Cell Trait, SCT) is extremely rare, creating a complex clinical paradox. The systemic hypercoagulability of SCA or SCT may, in some ways, **partially mitigate** the severe spontaneous bleeding typically seen in Hemophilia. However, this "antagonistic effect" is incomplete, as patients still face severe bleeding risks, particularly following trauma or surgery, such as prolonged post-circumcision bleeding. This confirms that the fundamental deficiency in secondary hemostasis (FVIII or FIX) remains the dominant pathology during high-stress hemostatic demands.

6.2 Therapeutic Dilemmas in Overlap Syndromes

Managing a patient with both a bleeding and a clotting disorder requires specialized, multidisciplinary care.

- **Hydroxyurea Use:** Hydroxyurea is a cornerstone therapy for SCA, successfully increasing fetal hemoglobin (HbF) and preventing acute vaso-occlusive events. However, its role and safety profile in patients with concomitant HA are not well-established in the literature.
- **The Balancing Act:** The core challenge is a profound therapeutic paradox: Factor replacement, mandatory for severe HA prophylaxis, inherently carries the risk of exacerbating the underlying hypercoagulable state of SCA. Clinicians must prioritize

effective Factor VIII prophylaxis to prevent crippling arthropathy and life-threatening hemorrhages, while continuously monitoring for thrombotic events.

6.3 Diagnostic Overlap in Acquired Syndromes

Clinical distinction between acquired syndromes like DIC and TMA, while critical for targeted therapy, can be difficult in critically ill patients. For example, cancer-related MAHA (CR-MAHA) can present with overlapping features, exhibiting MAHA and thrombocytopenia (suggesting TMA) alongside D-dimer elevation and factor consumption (suggesting DIC), yet having normal ADAMTS13 activity. The failure to rapidly achieve a definitive diagnosis often compels doctors to initiate high-risk therapies, such as PEX for possible TTP, given the near-100% mortality associated with delayed treatment.

Management Strategies (Medical, Surgical, Interventional Cardiology, Lifelong Follow-Up)

7.1 Management of Isolated Bleeding Disorders (Hemophilia and VWD)

- **Hemophilia:** Standard of care is Factor replacement therapy (prophylaxis) to prevent recurrent bleeding and joint damage. Emerging therapies include non-factor replacement agents and gene therapy, which aim toward a potential cure.
- **VWD:** Minor bleeding is often managed with desmopressin (DDAVP), which promotes the release of endogenous VWF and Factor VIII. Severe VWD or major surgical prophylaxis requires VWF/FVIII concentrates, often alongside antifibrinolytics like tranexamic acid for mucosal bleeds.

7.2 Management of Isolated Hemoglobinopathies (SCA)

SCA management focuses on disease modification. **Hydroxyurea** is crucial for increasing fetal hemoglobin (HbF), reducing acute crises, and improving chronic organ dysfunction. **Curative options** include Hematopoietic Stem Cell Transplantation (HSCT) and gene therapy, which address the root pathology.

7.3 Management of Acquired Overlap Syndromes (MAHA/TMA/PNH)

- **DIC:** The primary focus is immediate and aggressive treatment of the underlying precipitating condition (e.g., treating sepsis). Supportive care with blood products must be carefully balanced based on whether bleeding or clotting dominates.
- **TTP:** Acute TTP requires urgent, life-saving **Plasma Exchange (PEX)** combined with immunosuppression. The anti-VWF antibody **Caplacizumab** has significantly improved

outcomes by rapidly blocking VWF-platelet interaction.

- **PNH:** Management targets complement activation. The standard of care uses **C5 inhibitors** (Eculizumab, Ravulizumab), which block the late stage of the complement cascade and prevent red cell destruction. Newer oral therapies like **Iptacopan** block the alternative pathway earlier.

Lifelong Follow-Up and Prognosis

8.1 Chronic Complications and Surveillance

- **Hemophilia:** Requires lifelong monitoring for progressive joint destruction (arthropathy).
- **SCA:** Requires surveillance for chronic organ damage, including pulmonary hypertension, cardiac issues, and nephropathy, driven by chronic vascular injury.
- **PNH:** Even patients on complement inhibitors require long-term surveillance (typically every 6 to 12 months) for life-threatening complications, including bone marrow failure (MDS/AA) and major thrombosis.
- **8.2 Prognostic Benchmarks and Long-Term Morbidity**
- **DIC:** Mortality remains severely high, estimated to range between 45% and 78%, correlating strongly with the underlying condition.
- **TTP:** While acute mortality is substantially reduced to below 20% with timely Plasma Exchange , survivors face shortened overall survival and high rates of chronic morbidity, including depression (reported in 44% of patients), cognitive impairment, and new-onset hypertension. Routine screening for these psychological and cognitive long-term effects is now a critical part of TTP follow-up.
- **PNH:** Complement inhibitors have dramatically improved both life expectancy and quality of life.

8.3 Ethical and Regulatory Imperatives of Curative Therapies

The development of curative options like gene therapy for Hemophilia and SCA requires decades-long surveillance post-treatment, mandated by regulatory bodies (FDA and EMA), to detect potential late-onset adverse events such as secondary malignancy. This ethical necessity drives the need for global data coordination through registries to ensure population-level safety.

Methodology (Literature Review, Data Analysis, Expert Opinions, Case Studies, Comparative Analysis, Ethical Considerations)

This report is based on a systematic literature review encompassing established clinical guidelines and peer-reviewed articles detailing the pathophysiology, diagnostics, and treatment standards for Hemophilia, Sickle Cell Disease, DIC, TMA, and PNH. Data analysis involved the critical evaluation of key quantitative laboratory markers (ADAMTS13 activity, Fibrinogen, D-dimer) and the clinical application of established risk stratification models, including the ISTH DIC Scoring System and the PLASMIC Score, to illustrate rapid decision-making algorithms. The analysis incorporated case studies addressing the rare co-inheritance of Hemophilia and Sickle Cell disease, highlighting therapeutic conflicts and management dilemmas specific to dual pathologies. Comparative tabular data structures were utilized to synthesize key differential diagnostic criteria, emphasizing the laboratory distinction necessary for time-sensitive intervention in MAHA syndromes. Ethical considerations underscore the necessity of long-term surveillance following emerging genetic therapies.

CONCLUSION

Distinguishing between primary inherited bleeding disorders (Hemophilia) and chronic inherited hemolytic disorders with thrombophilia (SCA) is a process driven by recognizing their distinct core molecular faults: isolated clotting factor deficiency versus abnormal hemoglobin and vaso-occlusion.

The real diagnostic difficulty lies in the acute, acquired syndromes—DIC, TTP, and PNH—which dangerously combine severe hemolysis and coagulopathy. Successful management hinges on the urgent deployment of highly specific molecular tests (Factor Assays, ADAMTS13, Flow Cytometry) and validated clinical scoring systems (PLASMIC, ISTH score). These tools facilitate the immediate initiation of etiology-specific therapies, such as Factor replacement, Plasma Exchange, or complement inhibition, often in a high-stakes, time-critical environment.

The transition toward curative genetic therapies for inherited diseases underscores the importance of precise differential diagnosis to align treatment with molecular pathology. Concurrently, the necessity of decades-long safety surveillance following these transformative interventions emphasizes the growing intersection of clinical hematology, rigorous regulatory oversight, and bioethics in modern medicine.

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REFERENCES

1. Hemophilia - StatPearls - NCBI Bookshelf, https://www.ncbi.nlm.nih.gov/books/NBK551607/
2. Sickle Cell Anemia - StatPearls - NCBI Bookshelf, https://www.ncbi.nlm.nih.gov/books/NBK482164/
3. Disseminated Intravascular Coagulation and Acute Hemolysis - AAP Publications, https://publications.aap.org/books/chapter-pdf/779411/aap_9781581109689-part02-ch55.pdf
4. Thrombotic microangiopathies: a general approach to diagnosis and management - CMAJ, https://www.cmaj.ca/content/189/4/e153
5. Diagnosing Hemophilia - CDC, https://www.cdc.gov/hemophilia/testing/index.html
6. Advancements in complement inhibition for PNH and primary complement–mediated thrombotic microangiopathy - ASH Publications, https://ashpublications.org/bloodadvances/article/9/15/3937/537232/Advancements-in-complement-inhibition-for-PNH-and
7. Sepsis-associated disseminated intravascular coagulation and its differential diagnoses - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6528221/
8. Dual Hematologic Disorders in a Pediatric Patient: Hemophilia a and Sickle Cell Anemia – a Case Report - American Journal of Biomedical Science and Research, https://biomedgrid.com/pdf/AJBSR.MS.ID.003725.pdf
9. The hypercoagulable state in thalassemia - PubMed, https://pubmed.ncbi.nlm.nih.gov/11756150/
10. Hydroxyurea for People With Sickle Cell Disease | Nemours KidsHealth, https://kidshealth.org/en/parents/hydroxyurea.html
11. Sickle cell anemia - Symptoms & causes - Mayo Clinic,

https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876

12. Chronic Anemia - StatPearls - NCBI Bookshelf, https://www.ncbi.nlm.nih.gov/books/NBK534803/
13. Endothelium, Platelets, and Coagulation Factors as the Three Vital Components for Diagnosing Bleeding Disorders: A Simplified Perspective with Clinical Relevance, https://pmc.ncbi.nlm.nih.gov/articles/PMC9440837/
14. Von Willebrand disease - Diagnosis & treatment - Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/von-willebrand-disease/diagnosis-treatment/drc-20354984
15. Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6040080/
16. What connection can you make between sickle cell anemia and hemophilia? - CK-12, https://www.ck12.org/flexi/life-science/genetic-disorders/what-connection-can-you-make-between-sickle-cell-anemia-and-hemophilia/
17. Coagulation in the Pathophysiology of Hemolytic Anemias - ASH Publications, https://ashpublications.org/hematology/article-abstract/2007/1/74/19183
18. Sickle Cell Disease | Johns Hopkins Medicine, https://www.hopkinsmedicine.org/health/conditions-and-diseases/sickle-cell-disease
19. Disseminated Intravascular Coagulation (DIC) - Hematology and Oncology - Merck Manuals,https://www.merckmanuals.com/professional/hematology-and-oncology/coagulation-disorders/disseminated-intravascular-coagulation-dic
20. Disseminated intravascular coagulation (DIC): MedlinePlus Medical Encyclopedia, https://medlineplus.gov/ency/article/000573.htm
21. The hypercoagulable state in thalassemia | Blood | American Society of Hematology, https://ashpublications.org/blood/article/99/1/36/107240/The-hypercoagulable-state-in-thalassemia
22. TTP, HUS, AND DIC: Thrombotic Microangiopathies with a Side of Alphabet Soup, https://alliedhealth.lsuhsc.edu/CL/CE/Fall2022/BrunsonCLPCFall2022-TTP-HUS-AND-DIC.pdf
23. PLASMIC Score for TTP - MDCalc, https://www.mdcalc.com/calc/10200/plasmic-score-ttp
24. Thrombotic Thrombocytopenic Purpura or Disseminated Intravascular Coagulation? -

NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC5588493/

25. Post ASH 2022: Paroxysmal Nocturnal Hemoglobinuria and thrombotic microangiopathies, https://haema-journal.gr/?p=1884
26. Diagnostic and Prognostic Evaluation of Disseminated Intravascular Coagulation Using the Disseminated Intravascular Coagulation Index - MDPI, https://www.mdpi.com/2077-0383/14/21/7478
27. Performance of Large Language Models in Diagnosing Rare Hematologic Diseases and the Impact of Their Diagnostic Outputs on Physicians: Combined Retrospective and Prospective Study - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC12511990/
28. How I use hydroxyurea to treat young patients with sickle cell anemia - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC2902131/
29. HUS AND TTP - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC3972058/
30. Where have all the platelets gone? HIT, DIC, or something else? - ASH Publications, https://ashpublications.org/hematology/article/2023/1/43/506434/Where-have-all-the-platelets-gone-HIT-DIC-or
31. Anticomplement C5 therapy with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome - PubMed, https://pubmed.ncbi.nlm.nih.gov/25468487
32. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT - Frontiers, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2019.01157/full
33. Haemoglobinopathy and sickle cell disease - Discipline of Anaesthesiology, Pain Medicine & Critical Care, https://anaesthetics.ukzn.ac.za/Libraries/Documents2011/Haem_1a.pdf
34. Identifying Paroxysmal Nocturnal Hemoglobinuria With Flow Cytometry | Novartis, https://www.novartis.com/us-en/sites/novartis_us/files/identifying-paroxysmal-nocturnal-hemoglobinuria-with-flow-cytometry-brochure.pdf
35. Paroxysmal Nocturnal Hemoglobinuria - PNH | Choose the Right Test - ARUP Consult, https://arupconsult.com/content/paroxysmal-nocturnal-hemoglobinuria
36. Plasmic score applicability for the diagnosis of thrombotic microangiopathy associated with ADAMTS13-acquired deficiency in a developing country - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6517677/

37. Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome | Choose the Right Test - ARUP Consult, https://arupconsult.com/content/thrombotic-microangiopathies
38. Full article: Strategies to overcome the diagnostic challenges of autoimmune hemolytic anemias - Taylor & Francis Online, https://www.tandfonline.com/doi/full/10.1080/17474086.2023.2216930
39. How I manage severe von Willebrand disease - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6899759/
40. Diagnosis and treatment of thrombotic microangiopathy - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC9544907/
41. Disseminated Intravascular Coagulation - DIC | Choose the Right Test - ARUP Consult, https://arupconsult.com/content/disseminated-intravascular-coagulation
42. Paroxysmal nocturnal hemoglobinuria (PNH) Diagnosis & Treatment - NYC | Herbert Irving Comprehensive Cancer Center (HICCC) - New York, https://www.cancer.columbia.edu/cancer-types-care/types/rare-blood-disorders/conditions/paroxysmal-nocturnal-hemoglobinuria-pnh
43. Algorithmic Approach to the Diagnosis and Management of the Thrombotic Microangiopathies | American Journal of Clinical Pathology | Oxford Academic, https://academic.oup.com/ajcp/article/145/2/152/2195488
44. "Sickle cell trait and haemophilia: a rare association" - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC5987143/
45. Case Report: Microangiopathic Hemolytic Anemia With Normal ADAMTS13 Activity, https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2021.589423/full
46. PNH and Life Expectancy: Does the Disease Shorten Your Lifespan? - myPNHteam, https://www.mypnhteam.com/resources/pnh-and-life-expectancy-does-the-disease-shorten-your-lifespan
47. Hemophilia and Sickle Cell Disease - Duke Health Department of Rehabilitation Services, https://sites.duke.edu/ptot/pediatric-services/diagnosis-treated/hemophilia-and-sickle-cell-disease/
48. Thrombotic Thrombocytopenic Purpura - StatPearls - NCBI Bookshelf - NIH, https://www.ncbi.nlm.nih.gov/books/NBK430721/
49. MAHA, TTP, HUS, DIC... Oh My! Understanding Microangiopathic Hemolytic Anemias, https://www.tampaemergencymedicine.org/blog/maha-ttp-hus-dic-oh-my-understanding-microangiopathic-hemolytic-anemias

50. Distinguishing immune-mediated thrombotic thrombocytopenic purpura from septic disseminated intravascular coagulation using plasma levels of haptoglobin and factor XIII activity - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC9969072/
51. A Prospective Multicenter Study of Paroxysmal Nocturnal Hemoglobinuria Cells in Patients with Bone Marrow Failure - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC5594745/
52. Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations, https://pmc.ncbi.nlm.nih.gov/articles/PMC10112829/
53. Curative Therapies for Hemophilias and Hemoglobinopathies in Adults: Immune, Gene, and Stem Cell Approaches in a Global Context | MDPI, https://www.mdpi.com/2227-9059/13/8/2022
54. TTP: long-term outcomes following recovery - PMC - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC6246011/
55. Flow Cytometric Diagnosis of Paroxysmal Nocturnal Hemoglobinuria: Pearls and Pitfalls – A Critical Review Article - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6893893/
56. Hemophilia B gene therapy demonstrates long-term success, https://www.stjude.org/media-resources/news-releases/2025-medicine-science-news/hemophilia-b-gene-therapy-demonstrates-long-term-success.html
57. Development and application of machine learning models for hematological disease diagnosis using routine laboratory parameters: a user-friendly diagnostic platform - Frontiers, https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1605868/full
58. Paroxysmal Nocturnal Hemoglobinuria - Symptoms, Causes, Treatment | NORD, https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria