

Managing the Bleeding Patient

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ABBREVIATIONS: PT = prothrombin time; PTT = partial thromboplastin time.

INDEX TERMS: Anatomic hemorrhage; coagulopathy; systemic hemorrhage.

Clin Lab Sci 2003;16(2):107

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George A Fritsma is the Focus: Hemorrhagic Abnormalities guest editor.

Focus Continuing Education Credit: see pages 123 to 126 for learning objectives, test questions, and application form.

LEARNING OBJECTIVES (for the entire section)

The reader will be able to:

1. distinguish between anatomic and systemic hemorrhage.
2. distinguish between acquired and congenital hemorrhage.
3. select hemostatic laboratory tests that may be used to establish the presence of a hemostatic disorder.
4. identify hemostatic laboratory tests for use in pinpointing the cause of hemorrhage.
5. interpret the laboratory test profile results used to establish the presence of disseminated intravascular coagulation.
6. interpret the laboratory test profile results used to establish the presence of von Willebrand disease.
7. select single coagulation factor assays.
8. describe how to perform and interpret mixing studies.
9. determine the presence of a coagulation inhibitor.
10. select the appropriate coagulation factor concentrate therapy to treat hemorrhagic disorders.
11. calculate the correct dosage of coagulation factor concentrate to appropriately treat hemorrhagic disorders.

12. assess the dosage adequacy of the coagulation factor concentrate used to treat hemorrhagic disorders.
13. detail the selection and dosage of factor concentrates for von Willebrand disease, hemophilia, and hemophilia with the presence of an inhibitor.

The acute care hemostasis laboratory must be equipped to manage both acute and chronic hemorrhage. Hemorrhage is defined as bleeding that can be arrested only by special interventions such as pressure, elevation, ice, cauterization, ligation, or therapy.¹ Therapy may include non-biologic drugs such as DDAVP and Amicar, and coagulation concentrates in various forms. Hemorrhage may be *local or general, anatomic or systemic, acquired or congenital*. To establish the cause for a hemorrhagic event, the clinician first completes a history and physical examination, and then follows up with diagnostic laboratory tests.²

LOCAL VERSUS GENERAL HEMORRHAGE

Most bleeding is local. Hemorrhage from a single location signals a trauma, tissue necrosis, or a blood vessel defect. A surgical site may bleed because of an inadequately ligated or cauterized vessel. Local bleeding seldom implies a coagulopathy.

Bleeding is classified as general when it is excessive or when it originates from two or more sites (Table 1). Menorrhagia, hematemesis, epistaxis, bleeding from the gums, or bleeds into body cavities are signs of a hemostatic deficiency. Whenever such a coagulopathy is suspected, a careful workup involving hemostasis laboratory tests is essential.^{3,4}

ACQUIRED VERSUS CONGENITAL HEMORRHAGIC DISORDERS

Bleeding that first occurs in adulthood, is associated with a specific disorder (Table 2), and is not seen in kindred, implies an acquired hemorrhagic condition. When an adult patient presents with general hemorrhage, the physician first looks for an underlying disease, and then orders a hemostasis laboratory test profile.⁵

Congenital coagulopathies are uncommon, occurring in approximately one in 800 individuals, and are usually detected in infancy. Patients often have relatives with similar

Table 1. General hemorrhage symptoms that suggest a coagulopathy

Symptom	Comment
Excessive bleeding	Recurrent, delayed onset, bleeding from more than one site, bleeding that can be arrested only by a procedure or special treatment.
Menorrhagia	Heavy flow for more than three days, periods lasting more than seven days altogether
Epistaxis	Bleeding from both nostrils that requires packing
Hematemesis	
Bleeding from gums and mucus membranes	Visible petechiae and purpura in skin and mucus membranes

hemorrhagic symptoms. Hemorrhages may be spontaneous and may occur in unexpected locations such as joints, body cavities, retinal veins and arteries, or the central nervous system. Patients with mild congenital hemorrhagic disorders may have no symptoms until they reach adulthood or when they experience some physical challenge such as sports activity, a trauma, dental extraction, or surgery. The most common congenital deficiencies are von Willebrand disease, platelet function disorders, and factor VIII, IX, or XI deficiencies. Inherited fibrinogen, prothrombin, or factor V, VII, X, or XIII deficiencies are rare (Table 3).

ANATOMIC VERSUS SYSTEMIC HEMORRHAGE

General hemorrhage may be anatomic or systemic. Anatomic hemorrhage is seen in acquired or congenital *plasma procoagulant* deficiencies. When there is anatomic hemorrhage, bleeds may immediately follow traumatic events, but are often delayed or recurrent. Some bleeding is spontaneous. Most anatomic bleeds are internal: bleeding into joints, body cavities, or the central nervous system. Joint bleeds cause swelling, acute pain, and inflammation. Bleeds into soft tissues, such as muscles or fat, cause nerve compression and subsequent loss of function, temporary or permanent.⁶ Bleeds into body cavities cause symptoms related to the or-

Table 2. Disorders that cause a secondary coagulopathy

Disorder	Comment
End stage liver disease with hepatosplenomegaly	Thrombocytopenia, diminished vitamin K-dependent coagulants, dysfibrinogenemia, uncontrolled fibrinolysis
Uremia	Thrombocytopenia and qualitative platelet function loss
Malnutrition	Inadequate vitamin K intake resulting in decreased levels of vitamin K-dependent coagulants
Immune thrombocytopenia	Antibody-mediated platelet consumption, often drug-induced
Thrombotic thrombocytopenic purpura	Von Willebrand factor cleaving protease deficiency causes the presence of ultra high molecular weight von Willebrand factor multimers that trigger platelet consumption
Aplastic anemia, acute leukemia and myelodysplastic syndromes	Reduced platelet production
Myeloproliferative disorders	Increased platelet production with reduced platelet function
Disseminated intravascular coagulation	Triggered by septicemia, shock, inflammation, acute promyelocytic leukemia; evidenced by increased platelet consumption, loss of coagulation factors

gan that is affected, for instance, bleeding into the central nervous system causes headache, confusion, seizures, and coma; these must be managed as medical emergencies. Bleeds in the kidney cause hematuria and kidney failure.

Systemic, or mucosal, hemorrhage includes petechiae, purpura, easy bruising, epistaxis, menorrhagia, hematuria, hematemesis, and gingival bleeding. Systemic hemorrhage associates with *thrombocytopenia, qualitative platelet disorders, mild or moderate von Willebrand disease, or vascular disorders such as telengectasia*. A careful history and physical examination may distinguish between anatomic and systemic bleeding; the distinction helps direct investigative testing and treatment.

Liver disease, severe von Willebrand disease, and DIC are accompanied by both anatomic and systemic bleeding. Uremia usually causes systemic bleeding and malnutrition, anatomic bleeding.

LABORATORY TESTS IN GENERAL HEMORRHAGE

Please refer to the accompanying article in this issue by Laura J Taylor, "Laboratory Management of Hemorrhage" for a discussion of hemostasis laboratory testing for the bleeding patient.

When the history and physical examination lead the physician to suspect a hemostatic disorder, the three primary assays used are prothrombin time (PT), partial thromboplastin time (PTT), and platelet count (Table 4). When there is anatomic hemorrhage and either the PT or PTT result is

prolonged to 1.5 times the mean of the reference interval, a procoagulant deficiency or specific inhibitor is suspected and follow-up work begins. Mixing studies and factor assays help establish the cause for bleeding, most often an acquired multiple factor deficiency or an antibody such as anti-VIII. The thrombin clotting time is used in to rule out plasma heparin, often unreported.

Systemic bleeding accompanied by a platelet count less than $50 \times 10^9/L$ prompts follow-up testing for thrombocytopenia, whereas if the count is $150 \times 10^9/L$ or higher, von Willebrand disease or a qualitative platelet abnormality is suspected.

When bleeding is both systemic and anatomic, and the platelet count is below the established reference interval, disseminated intravascular coagulation may be confirmed by fibrinogen and D-dimer assays.

TREATMENT OF GENERAL HEMORRHAGE

Please refer to the accompanying article in this issue by Margaret G Fritsma, "Use of Blood Products and Factor Concentrates for Coagulation Therapy" for a discussion of the use of plasma and factor concentrates.

If the cause for the general hemorrhage is multiple factor deficiency as may be seen in liver disease, the treatment is fresh frozen plasma or, in limited cases, cryoprecipitate (Table 5). Platelet concentrate is used when the platelet count drops to life-threatening levels, typically below $20 \times 10^9/L$, though some physicians use $10 \times 10^9/L$.

Table 3. Congenital bleeding disorders

Disorder	Comment
Von Willebrand disease	Present in 1 in 1000 individuals. Levels of von Willebrand factor are 20% lower in blood group O than in the other groups
Congenital thrombocytopenia	Relatively common but poorly defined
Congenital platelet function disorders	Rare, prevalence has not been computed
Factor VIII deficiency	1 in 5000 live male births
Factor IX deficiency	1 in 30,000 live male births
Factor XI deficiency	Over half of cases described in Jews; the Ashkenazi Jews of Israel have a frequency of 1:8.
Fibrinogen, factor II, V, VII, X, or XIII	Rare deficiencies

Severe von Willebrand disease requires fractionated factor VIII concentrates that contain von Willebrand factor, whereas the acute bleeding associated with hemophilia requires single factor concentrates prepared either by monoclonal plasma purification or recombinant manufacturing techniques. When an inhibitor to a coagulation factor such as anti-factor VIII, is detected, prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa are effective.

COMMUNICATION BETWEEN THE CLINICIAN AND THE LABORATORY

Clinical decision-making is based upon established practice models. An academic approach to clinical practice provides a useful framework. Nevertheless, clinical situations arise in which individualized judgment is essential. Refer to the accompanying article in this issue by Marisa B Marques MD titled "Treatment of Single Factor Deficiencies: A Case-Study Approach" for a practical look at the clinical management of hemorrhage. The successful man-

agement of the bleeding patient ultimately depends upon full communication among the clinician, the hemostasis laboratory, and the transfusion service.

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Table 4. Laboratory tests in hemorrhage

Primary Tests	PT, PTT, Platelet count
Multiple coagulation factor deficiency	Mixing studies, factor assays, thrombin time, platelet count
Thrombocytopenia	Bone marrow examination, platelet antibodies
Qualitative platelet disorder	Platelet aggregometry, PFA-100
Von Willebrand disease	VWF activity, VWF antigen, and factor VIII
Disseminated intravascular coagulation	Fibrinogen, D-dimer

Table 5: Treatment of general hemorrhage

Multiple factor deficiency secondary to liver disease, renal disease, or malnutrition	Fresh frozen plasma, cryoprecipitate
Thrombocytopenia	Platelet concentrate
Von Willebrand disease	Fractionated plasma factor VIII preparations
Single factor deficiency (hemophilia)	Monoclonally purified plasma-derived factor concentrate; recombinant factor concentrate
Factor inhibitor	Prothrombin complex, activated prothrombin complex, recombinant activated factor VII