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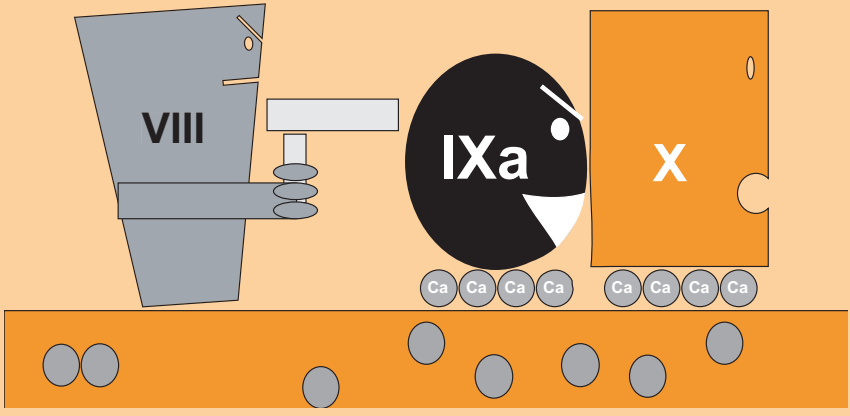
2nd Edition



Thomas G. DeLoughery

v a d e m e c u m

Hemostasis and Thrombosis

2nd Edition

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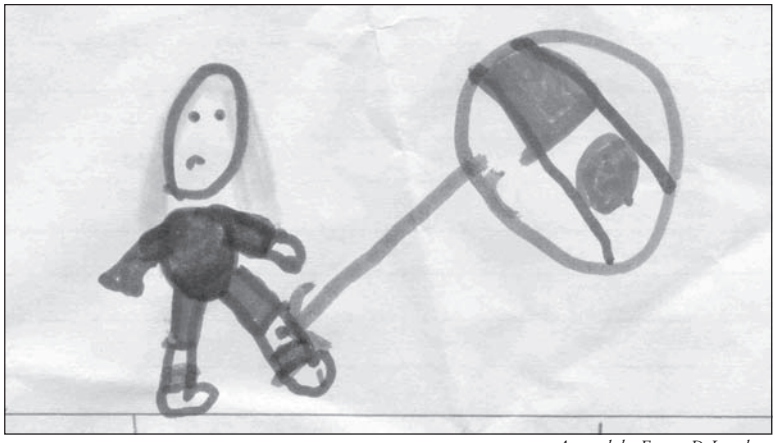
Dedication

To my wife Jean and my daughter Emma



Artwork by Emma DeLoughery

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Preface

This handbook is designed to be a resource for both the common and uncommon hemostatic problems that health care providers often face in clinical practice. The handbook was written to offer a practical guide to recognizing, diagnosing, and managing these patients. Since the first edition many changes have occurred in hemostasis and thrombosis which require a new edition.

One of the most remarkable areas of medicine continues to be the revolution in management thrombotic diseases. This includes the introduction new anticoagulants and the results of many randomized clinical trials. A large portion of this book is dedicated to the thrombotic disorders and their therapy. This book has tried to be as up-to-date as possible with many of the novel antithrombotic agents that are being introduced on the market today. I have also added a chapter on Pediatric thrombosis given the increasing recognition of this problem.

I hope this book will not only help in the management of patients with disorders of hemostasis but will encourage the read to learn more about one of the most fascinating areas of medicine. I encourage the reader to take advantage of the general references listed after the first chapter and the reference listed after each chapter to acquire deeper knowledge.

Thomas G. DeLoughery, M.D.

Acknowledgments

I would like thank my wife Jean for reading, editing, and making many helpful comments on the manuscript. I would also like to thank Robina Ingram-Rich and Sandra Puckett for their helpful comments on the hemophilia chapter.

I would like to thank my colleagues and fellows for always teaching and challenging me. I would particularly like to thank Jody Kujovich, Lynn Boshkov, Deborah Robertson, and David Sauer for their help and comments.

I would finally like to thank Ron Landes for giving me the honor of once again writing a book on my favorite subject for his company.

CHAPTER 1

Basics of Coagulation

The basic mechanics of hemostasis must be grasped in order to understand the disorders of hemostasis and the therapies designed to alter coagulation. Generally, coagulation is divided into fibrin formation, fibrinolysis, platelet function, and natural anticoagulants.

Formation of Fibrin

The coagulation cascade is a series of enzymatic steps designed to amplify the insult of initial trauma into the formation of a fibrin plug. Recent research has revealed how fibrin formation occurs in vivo rather than how it occurs in the test-tube. The in vivo pathway for the purposes of this book is called the "new pathway" of coagulation. Unfortunately, the two most common laboratory tests for coagulation and many books are still based on the test-tube models of coagulation. It is important to learn (a little bit) about the older models of coagulation to understand these two laboratory tests and much of the classic literature.

The Old Pathways (Fig. 1.1)

In the test tube tissue factor (TF)+VIIa is much more effective in activating factor X than factor XI. This pathway is initiated by adding bits of tissue ("tissue thromboplastin", usually minced animal's brains) to plasma. The brain tissue is used in these studies because it is an excellent source of both phospholipids and tissue factor. Since an extrinsic initiator, brain, was added, this pathway is known as the "*extrinsic pathway*." The second pathway is started when blood is exposed to glass. Since nothing is added (except the glass surface) this is called the "*intrinsic pathway*." This pathway is dependent on a different set of enzymes that result in factor XII activating factor XI. Since both pathways are the same once Factor X is formed, the path from factor X to fibrin formation is known as the "common" pathway.

To recap:

Extrinsic pathway: **TF+VIIa**→Xa+V→IIa→Clot
Intrinsic pathway: **Contact system→IXa+VIII**→Xa+V→IIa→Clot
Common pathway: **→Xa+V→IIa→Clot**

These pathways explained laboratory findings but did not match clinical observations. Patients with deficiencies of the contact system did not bleed, suggesting that the intrinsic pathway was not relevant. Hemophiliacs, on the other hand, are missing proteins VIII and IX (intrinsic pathway), which implies that the extrinsic pathway alone was not enough to support hemostasis. These contradictory observations led to the development of the "new pathway".

The Players

Most of the coagulation proteins are either enzymes (serine proteases) or cofactors (Table 1.1). A coagulation protein is a framework consisting of a serine protease

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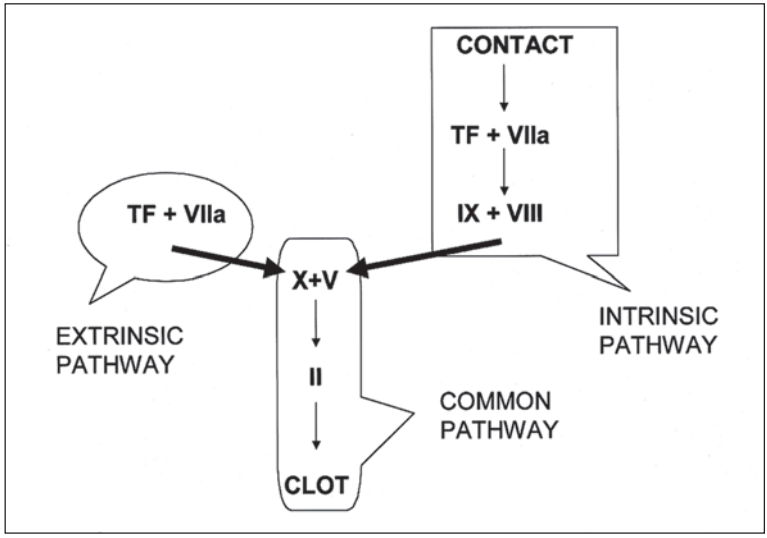


Fig. 1.1. Old Models of Coagulation.

with different protein domains added to it. The purpose of these domains is to add different capabilities to the clotting proteins.

Factors II, VII, IX, X, protein C, protein S and protein Z have vitamin K- dependent glutamic acid (GLA) domains on the amino terminus of the protein. These domains contain 9-11 glutamic acids modified to form gamma-carboxyglutamic acid (GLA). This modification allows calcium to bind to these proteins. The binding of calcium changes the conformation of the protein and serves to bind them in turn to phospholipid surfaces (Fig. 1.2). The hepatic GLA redox reaction is dependent on vitamin K ("Koagulation"). Without this vitamin, dysfunctional coagulation proteins are produced which function poorly in coagulation reactions. The drug warfarin blocks the recycling of vitamin K and leads to a reduction in functional coagulation factors.

Table 1.1 Coagulation proteins

Enzymes	**Cofactors**	**Miscellaneous**
Factor IIa	Tissue factor	Fibrinogen
Factor VIIa	Factor V	Factor XIII
Factor IXa	Factor VIII	$Alpha_2$antiplasmin
Factor Xa	Protein S	PAI-1
Factor XIa		Antithrombin
Protein C		
tPA		
Plasmin		

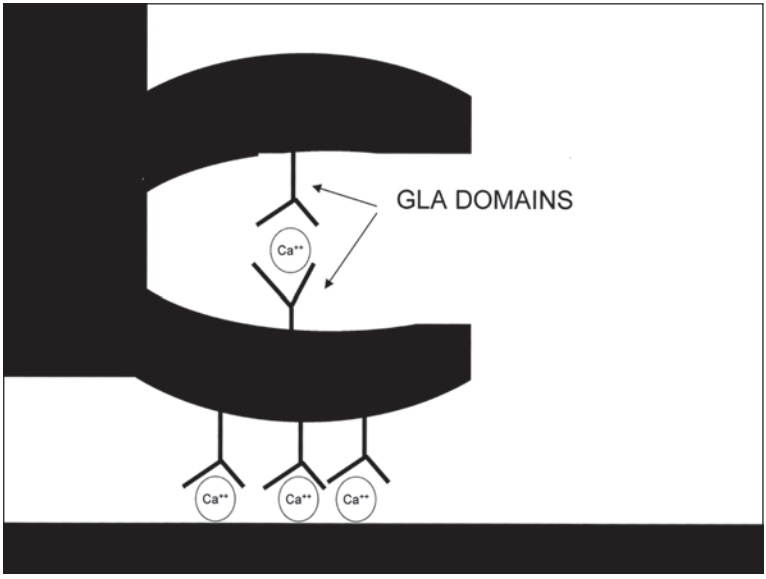


Fig. 1.2. GLA domains serves two functions. One is to bind the protein to phospholipid surfaces. The other is to fold the protein into the proper configuration.

Factor II, tissue plasminogen activator, and plasmin contain "kringle" regions (named after a Danish pastry). The kringle domains help these proteins bind to fibrinogen (Fig. 1.3).

The cofactors V and VIII are very similar molecules and require activation by thrombin. The mechanism underlying their cofactor function is unknown. The presence of these two cofactors enhances the efficiency of the coagulation factors by at least 100,000-fold.

The "Quaternary Complex"

Most coagulation reactions have four components, starting with the enzyme binding to a cofactor that is bonded by calcium to a surface (Fig. 1.4). This serves to make a little "coagulation factory" on the surface and improves the efficiency of the reaction by bringing the components together.

- **Enzyme**: (VIIa, XIa, Xa, IIa, protein C)
- **Co-factor**: (V, VIII, tissue factor, protein S)—speeds up reactions by orders of magnitude
- **Calcium**: binds protein to surfaces
- **Phospholipid surface**: Has a negative charge and speeds reactions by bringing proteins closer to each other.

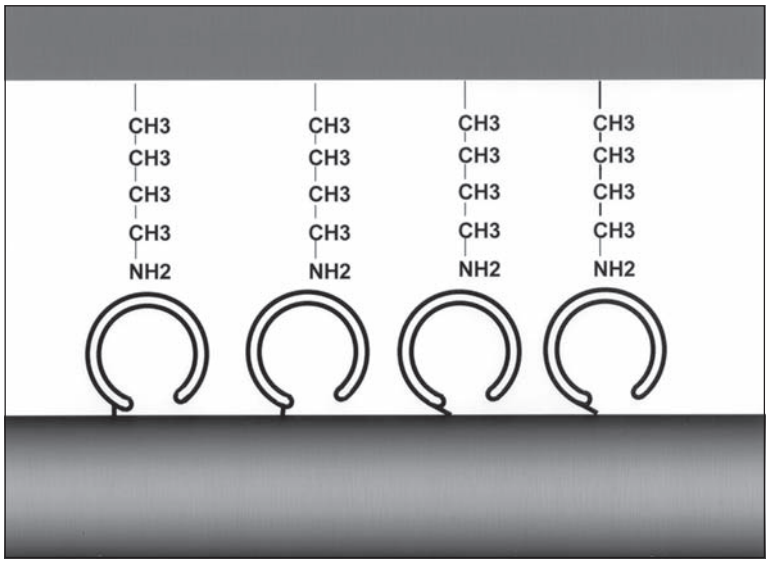


Fig. 1.3. Binding of the "Kringle" region to the lysine residue of fibrinogen.

Fig. 1.4. The quartanry complex. Active Enzyme (IXa) activates proenzyme (X) with the help of a co-factor (VIII). These enzymes are bound to the phospholipid surface by calcium.

Initiation of Coagulation

Overview: TF+VII→IX+VIII→X+V→II

The key step in the initiation of coagulation is exposure of tissue factor (TF). TF is a transmembrane surface molecule that is more or less on all cell surfaces except endothelial cells and circulating blood cells. Thus, flowing blood under normal

Table 1.2 Key coagulation reactions

Key Reactions

The New Pathway

TF+VIIa➞IXa+VIII➞Xa+V➞IIa➞Clot

The Old Pathway

Intrinsic pathway: **Contact system ➞IXa+VIII**→Xa+V→IIa→Clot

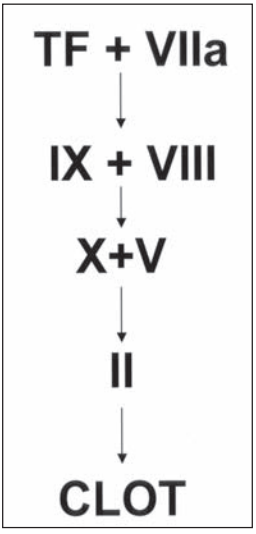
Extrinsic pathway: **TF+VIIa**→Xa+V→IIa→Clot

Common pathway: **➞Xa+V➞IIa➞Clot**

Fibrin Formation

Fibrinogen-(*THROMBIN*)→Fibrin monomer→Fibrin polymer -(*FACTOR XIII*)→Fibrin Clot

Fig. 1.5. New standard model for coagulation.



conditions is never exposed to TF. With trauma, blood spills out of the vessel and contacts TF. This is what initiates the coagulation cascade.

TF binds factor VII. This reaction would stop immediately without active factor VII (VIIa) to cleave factor IX (Fig. 1.6). However a tiny bit (0.1%) of factor VII circulates in the active form. This bit of VIIa from the blood binds TF, the TF-VIIa complex activates surrounding TF-VII complexes and these complexes start converting factor IX into IXa (Fig. 1.5).

Now factor IXa, with its cofactor VIIIa, converts X into Xa. The presence of VIIIa is crucial for the function of the Xa complex. Of note, the underlying pathology of the two most common forms of hemophilia is the absence of the two proteins in this reaction (IX and VIII) (Fig. 1.7).

Fig. 1.6. Tissue factor is exposed and binds to factor VIIa. The tissue factor-VIIa complex then activates factor IX.

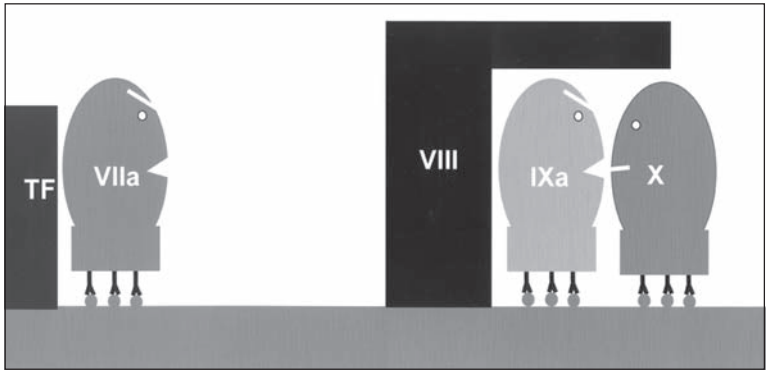


Fig. 1.7. Factor IX along with its cofactor VIII activates factor X.

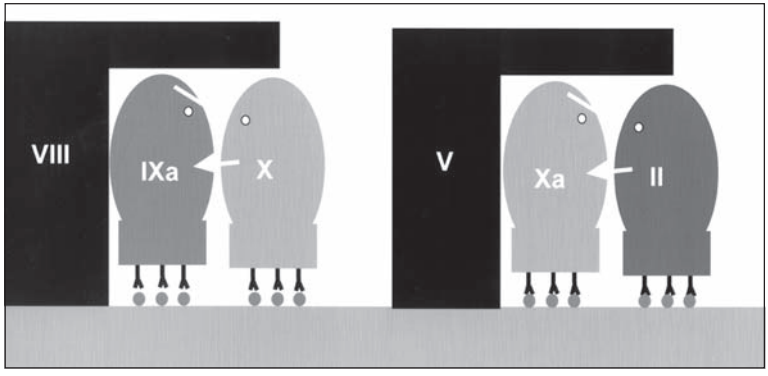


Fig. 1.8. Factor X along with its cofactor factor V activation prothrombin into thrombin.

Factor Xa binds with cofactor Va to generate thrombin (IIa) from prothrombin (II). The production of thrombin is the final step in the initiation of coagulation and is the single most crucial step in hemostasis (Fig. 1.8).

Thrombin

Thrombin is a multifunctional molecule. It functions to:

- Cleave **fibrinogen** into fibrin
- Activate **factors V and VIII**
- Activate **factor XIII**
- Activate **factor XI**
- Activate **platelets**
- Activate **thrombin activatable fibrinolysis inhibitor (TAFI)**
- Activate **fibrinolysis**
- Activate **protein C**

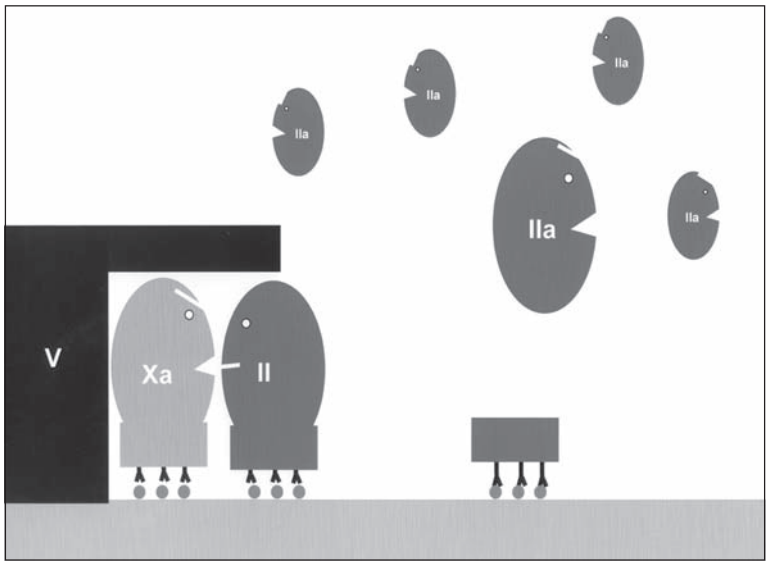


Fig. 1.9. Thrombin, freed from its GLA domains, flees to performs its many functions.

Thrombin is unique in several ways (Fig. 1.9). It does not require a co-factor for enzymatic function. When it is activated, it separates from its GLA domain so it can float around to promote clotting. Thrombin also provides both *positive feedback* by activating factors V, VIII, XI, XIII, TAFI and *negative feedback* by activating protein C and promoting fibrinolysis. Thrombin activation of factor XI provides a further positive feedback loop. Active factor XI activates IX eventually leading to more thrombin generation.

Fibrin Formation (Figs. 1.10, 1.11)

Fibrin is formed by turning soluble circulating fibrinogen into an insoluble fibrin thrombus. This is done in two steps. In the first step thrombin converts fibrinogen into fibrin monomers which spontaneously polymerize to form fibrin polymers. In the second step factor XIII stabilizes the clot by forming amide bonds between different fibrin polymers:

Fibrinogen→Fibrin monomer→Fibrin polymer→Fibrin clot

Thrombin acts on fibrinogen and clips off two peptides (fibrinopeptide A and B). This produces the *fibrin monomer*. The act of thrombin clipping off these peptides exposes polymerization sites that can bind to other fibrin monomers. The monomers polymerize together to form a loose clot. *Factor XIII* then solidifies the bond by forming glutamyl-lysine bridges between the side chains of the fibrin monomers. Note that factor XIII is the only coagulation enzyme that is *NOT* a serine protease.

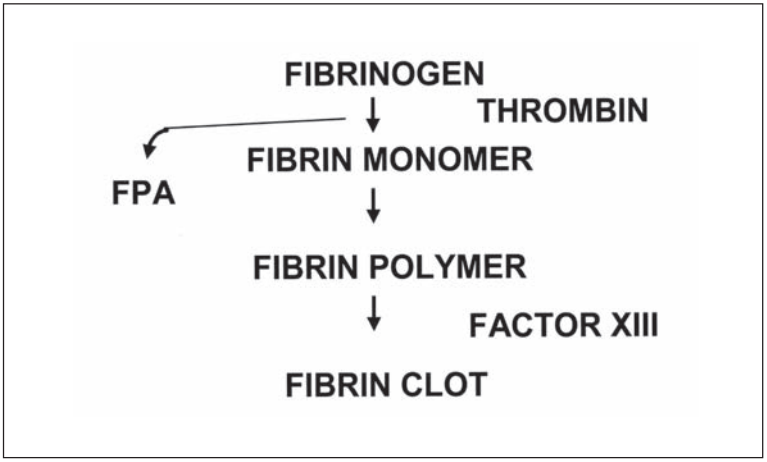


Fig. 1.10. Formation of the fibrin clot.

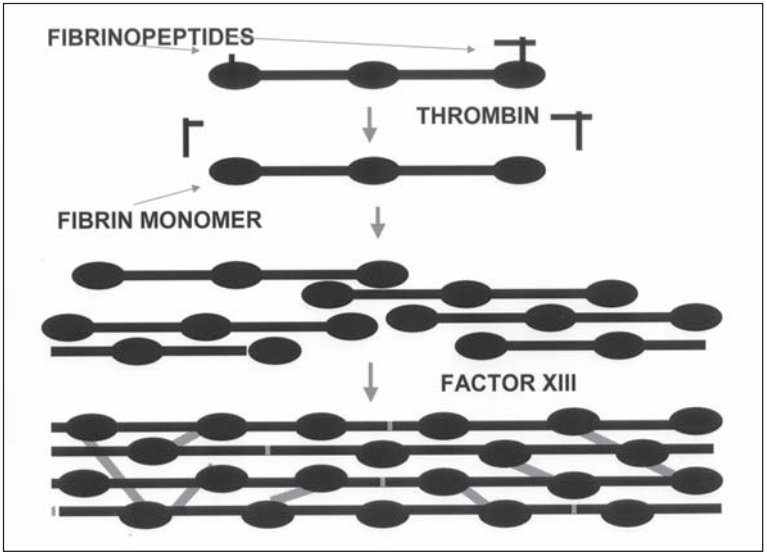


Fig. 1.11. Formation of the fibrin thrombus. Thrombin acts on fibrinogen to cleave fibrinopeptide A and B. This forms the fibrin monomer that loosely polymerizes. Factor XIII covalently bonds the fibrin monomer to form a stable thrombus.

In addition thrombin promotes coagulation by activating thrombin activatable fibrinolysis inhibitor (TAFI) (Fig. 1.12). TAFI cleaves the lysine residues to which many fibrinolytic enzymes bind, rendering the clot less likely to be dissolved.

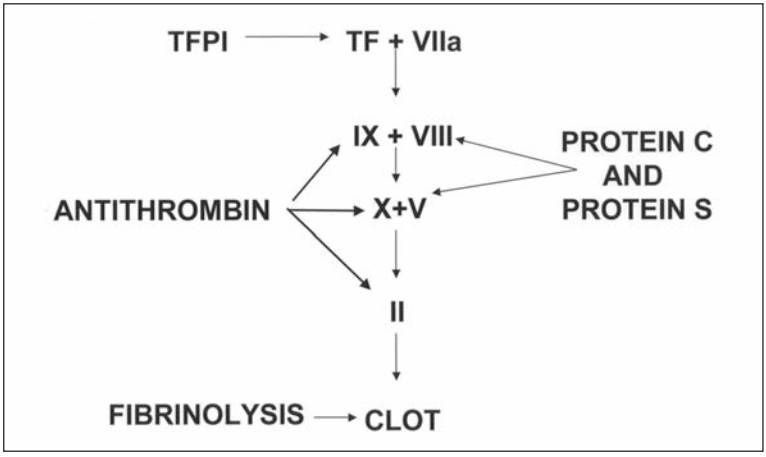


Fig. 1.12. Natural anticoagulants.

The Role of Factor XI

The "new" pathway leaves out the role of several proteins found in the older pathways. The contact system (factors XII, etc..) appears to play a role in inflammation but patients with deficiency of these proteins do not have hemostatic defects. The role of factor XI is more confusing. Although not in the new pathway, patients with deficiencies of factor XI do exhibit bleeding, especially after surgery. Thrombin can activate factor XI which then feeds back to activate factor IX. This then leads to more thrombin generation. More thrombin formation leads to activation of TAFI. This theory is consistent with the finding that patients lacking factor XI often have bleeding in sites of fibrinolytic activity such as the mouth after oral surgery.

Fibrinolysis

The fibrinolytic system is responsible for breaking down blood clots once they have formed. Obviously this is an important process to prevent thrombi from getting too large, to aid wound healing, and to prevent thrombosis in an undesirable place. Recent research has also implicated roles for proteins from the fibrinolytic system in diverse processes such as cancer metastasis and memory.

Fibrinolytic Proteins

The key proteins in the fibrinolytic system are (Fig. 1.13):

Plasmin

This is a serine protease produced by the liver which cleaves bonds in fibrin

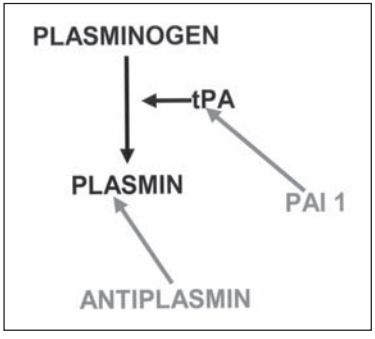


Fig. 1.13. The fibrinolytic pathway.

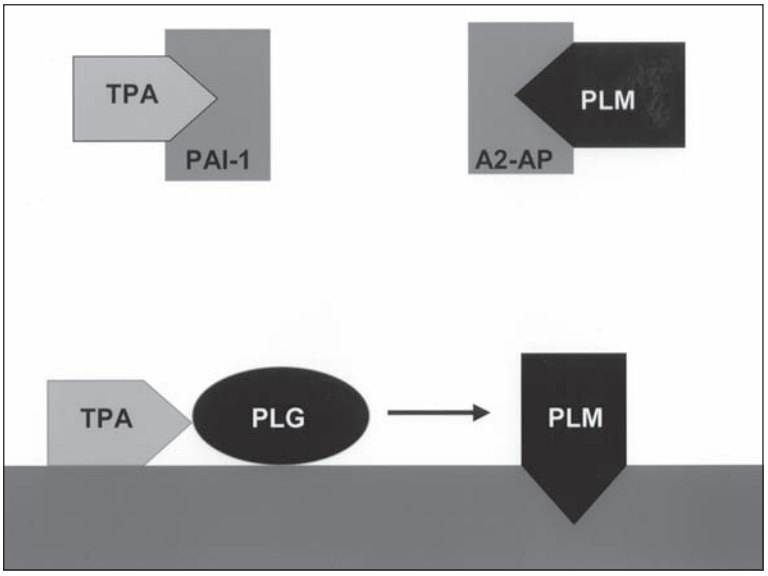


Fig. 1.14. Physiologic fibrinolysis. Free tPA can bins to fibrin and efficiently activate plasminogen to plasmin. Any free tPA or plasma is inactivated by circulating inhibitors.

and fibrinogen. Normally it circulates as an inactive precursor *plasminogen*, but it can be converted to plasmin by:

Tissue plasminogen activator (tPA): This is produced by endothelial cells. tPA is the physiologic activator of plasminogen.

Urokinase (UK): This is secreted in the urine (hence its name) and in many other cells. It is also a potent activator of plasminogen.

Several inhibitors of fibrinolysis are present to keep the fibrinolytic system in balance:

Plasminogen activator inhibitor (PAI-1): PAI-1 is made by the liver and endothelial cells. It binds and inactivates tPA.

Alpha$_2$ antiplasmin: This is made by the liver. It binds and inactivates plasmin.

Fibrinolysis—The Process

The ability of tPA to cleave plasminogen to plasmin is far greater when plasminogen and tPA are *both bound* to the fibrin clot. Moreover, when plasmin is bound to fibrin, it is protected from the action of circulating alpha$_2$-antiplasmin (Fig. 1.14).

A formed thrombus carries with it the seeds of its own destruction by incorporating plasminogen into the clot. tPA released from nearby endothelial cells percolates into the clot. The tPA binds to fibrin and then converts plasminogen to plasmin, which lyses the clot. Any excess tPA that escapes into the plasma is rapidly inactivated by PAI-1. Any plasmin that escapes in the plasma is rapidly inactivated by alpha$_2$-antiplasmin. Thus, active fibrinolysis is confined to the thrombus itself (Fig. 1.15).

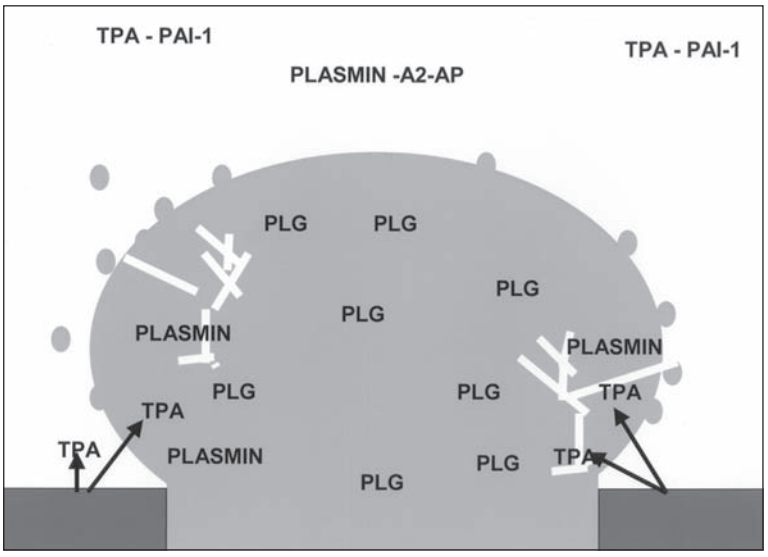


Fig. 1.15. When the thrombus reaches normal endothelial cells, the endothelial cells will secrete tPA that binds to the fibrin and cleaves plasminogen to plasmin lysis the thrombus.

Platelet Production and Life Span

Platelets are made in the bone marrow. Huge cells known as megakaryocytes (derived from hematopoietic stem cells) are the precursors to platelets; one megakaryocyte can produce 2,000 platelets. Platelets bud off the edges of the megakaryocytes and the megakaryocyte eventually perishes by evaporating. The platelet circulates in the blood for 7-10 days. Platelets either circulate freely or are sequestered in the spleen. At any given time one-third of the platelets are located in the spleen.

Thrombopoietin (TPO)

Discovered in 1994, TPO is the main growth and maturation factor for megakaryocytes. One-half of the TPO molecule is very similar to erythropoietin. TPO can make early precursor cells differentiate into megakaryocytes and can also induce generation of platelets by megakaryocytes. TPO and molecules with TPO-like activity are currently being tested in patients with severe thrombocytopenia due to chemotherapy or bone marrow transplantation.

Function of Platelets

Platelets do four things:

1. **Adhere** to damaged endothelium.
2. **Store** ADP and proteins.
3. **Aggregate** with other platelets.
4. **Provide a surface** for coagulation reactions.

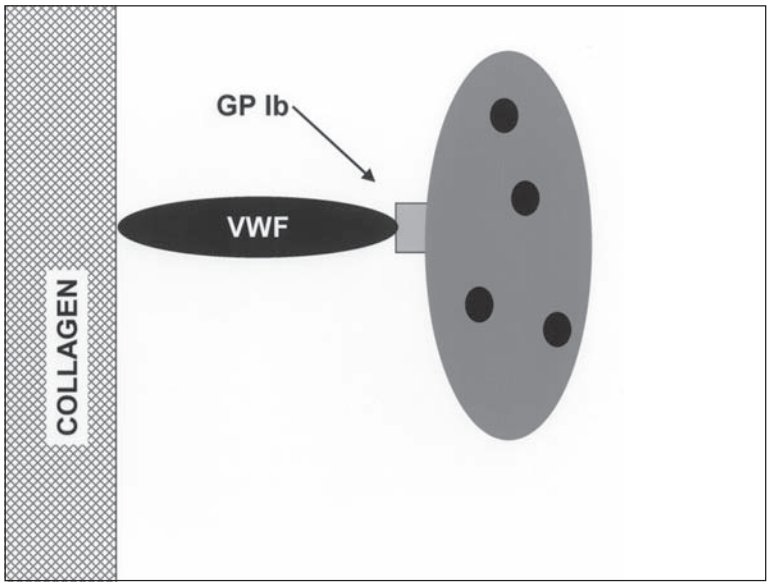


Fig. 1.16. Platelet adhesion: Platelet binding to collagen with von Willebrand factor as the glue and GP Ib as the receptor.

Platelet Adhesion (Fig. 1.16)

Damage to a blood vessel exposes *collagen* that is wrapped around the vessel. The exposed collagen reacts with and binds a large multimeric protein known as *von Willebrand factor*. Once it is bound, von Willebrand factor changes in conformation at one end so that it now can bind to platelets. The von Willebrand factor attaches to the platelet receptor *glycoprotein (Gp) Ib*. Platelet adhesion by von Willebrand factor creates a platelet monolayer over an injured surface. The binding of von Willebrand factor to Gp Ib leads to physiological changes called platelet activation.

About von Willebrand Factor

Von Willebrand Factor (vWF) is a huge molecule, up to 20 million daltons in molecular weight. It serves another role in hemostasis by carrying and protecting coagulation factor VIII. Patients who completely lack vWF also lack factor VIII, which results in a severe bleeding disorder.

Summary of Platelet Adhesion

Platelet adhesion occurs by exposing *collagen*, which leads to the binding of *von Willebrand factor* ("the glue") to the platelet receptor *GP Ib*.

Platelet Storage (Figs. 1.17, 1.18)

Platelets are filled with granules that store ADP and other proteins released when platelets are activated. *Alpha* granules store proteins and *dense* granules store chemicals. Alpha granules contain proteins such as vWF and factor V. *Dense* granules

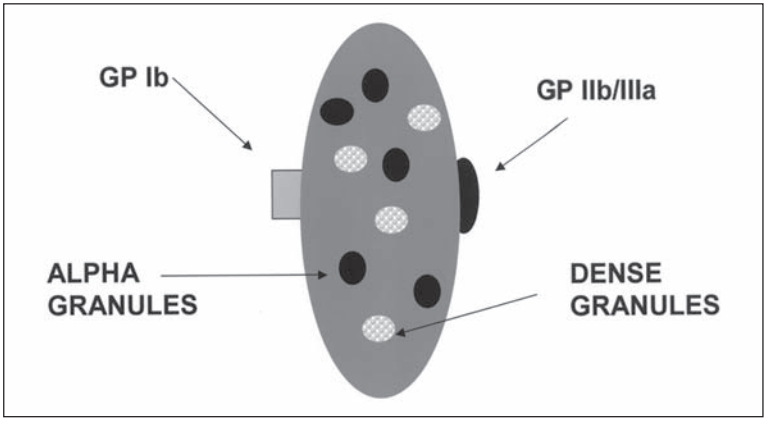


Fig. 1.17. Platelet structure demonstrating two key receptors: GP Ib and IIb/IIIa and two granules—The alpha granules and dense granules.

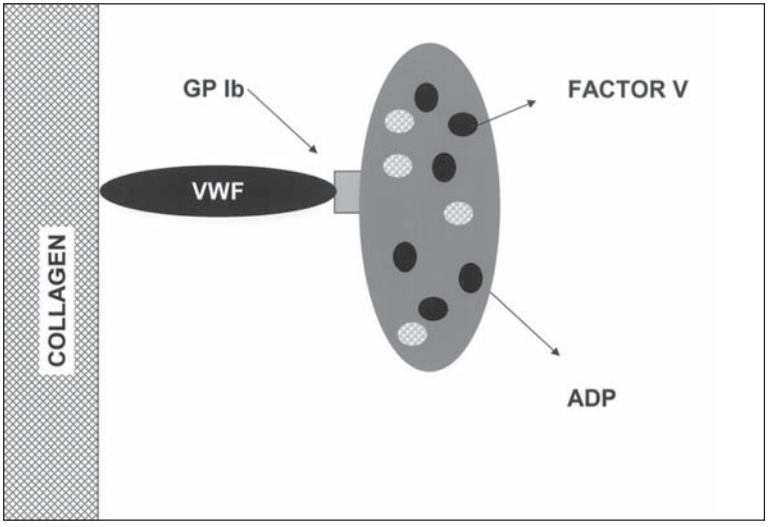


Fig. 1.18. Platelet, when activated, releases its granule contents.

contain chemicals such as serotonin and ADP which, after release, activate nearby platelets. Platelet activation also leads to production of thromboxane A_2, a key activator of platelets (recall that thromboxane A_2 synthesis is blocked by aspirin).

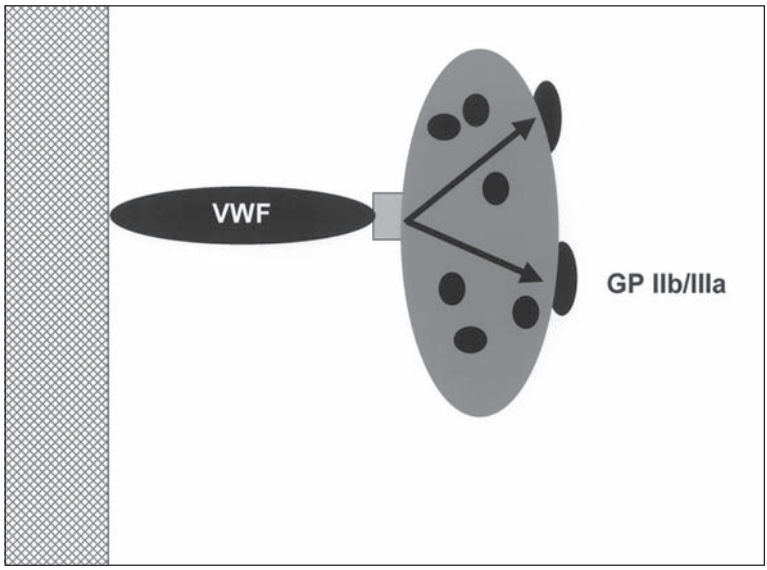


Fig. 1.19. Binding of von Willebrand factor to GP Ib initiating platelet activation and exposing GP IIb/IIIa.

Platelet Aggregation (Figs. 1.19, 1.20)

Platelet aggregation is the binding of platelets to *each other* (as opposed to adhesion where platelets *adhere* to the *vasculature*). Aggregation occurs because of the activation of a platelet receptor known as *GP IIb/IIIa*. This platelet receptor is activated by a number of processes including:

1. Binding of *vWF* to *Gp Ib*.
2. Binding of *platelet agonist* such as thromboxane A2 and ADP to platelet receptors.
3. Binding of *thrombin* to the platelet thrombin receptor. This ties the humoral phase of coagulation (tissue factor etc.) to platelet activation. Thrombin is the *MOST* potent physiologic activator of platelets known.

Activation of GP IIb/IIIa is the final common pathway for platelet aggregation. The GP IIb/IIIa receptor is a target for many powerful antiplatelet agents currently in use.

After the platelets have formed a monolayer on an injured surface, they release platelet agonists such as ADP. This activates nearby platelets causing them to activate their own GP IIb/IIIa. Fibrinogen (abundant in the plasma) then binds to all the active Gp IIb/IIIa exposed on the platelet surface. The "*glue*" for platelet aggregation is *fibrinogen*. This acts to clump platelets together into a large mass, forming a platelet plug that stops the bleeding.

Platelet Surface

Coagulation reactions take place on *surfaces*. This allows all the coagulation factors to be close to one another and increases the efficiency of the reactions. When

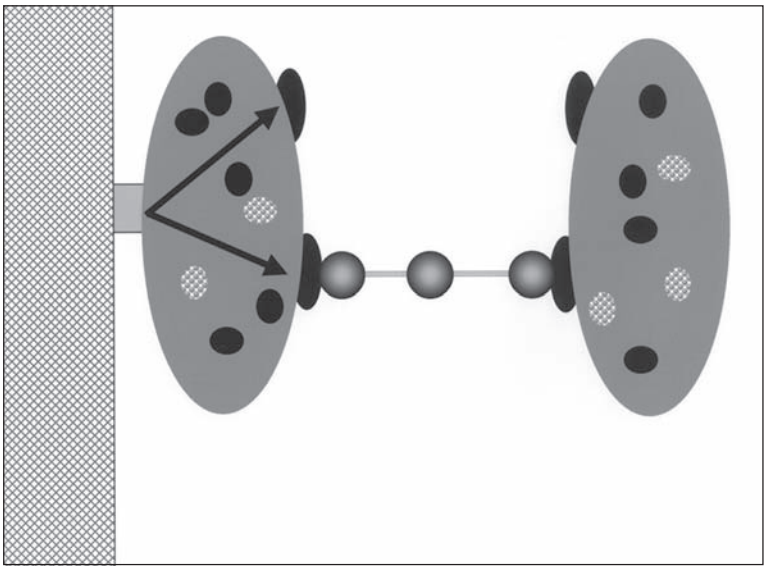


Fig. 1.20. Platelet aggregation: Binding platelet to platelet with fibrinogen as the glue and GP IIb/IIIa as the receptor.

platelets are activated, they expose a negatively charged phospholipid—*phosphatidylserine*.

Phosphatidylserine augments the binding of coagulation factors to injured surfaces. Since platelets are found at the site of injury, their surfaces provide a platform for coagulation. When platelets are activated, little blebs (called platelet *microparticles*) bubble off the surface. These microparticles increase the surface area available for coagulation reactions many times over.

Natural Anticoagulants

For every step of the coagulation cascade there exists a protein inhibitor of that step. These proteins ensure that excess thrombosis does not occur. These proteins are tissue-factor pathway inhibitor (TFPI), antithrombin (formally known as antithrombin III), protein C and protein S.

Tissue-factor pathway inhibitor is a protein that binds to factor Xa. This complex then forms a quarternary complex with tissue factor-VIIa and halts further IXa formation. It is speculated that coagulation continues via thrombin activating factor XI which in turns activates factor IX and leads to more thrombin generation.

Protein C is a serine protease that cleaves and destroys factors Va and VIIIa. Its cofactor protein S is crucial for this function. Both proteins C and S are vitamin K dependent. Protein S has several unusual features. First, it is not a serine protease. Secondly, it circulates in two forms in the plasma, a free form and a form bound to C4B-Binding protein. Only the free form can serve as a cofactor to protein C. Normally about 40% of protein S exists in the free form. Alterations in this ratio, either acquired or genetic, are responsible for many of the hypercoagulable states.

Antithrombin is a serine protease inhibitor that binds and inactivates all the serine proteases of the coagulation cascade. Its function is greatly augmented by either natural heparan or exogenous heparin. The addition of these complex polysaccharides leads to a dramatic increase in antithrombin's ability to bind and neutralize serine proteases.

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CHAPTER 2

Tests of Hemostasis and Thrombosis

"A routine laboratory test once well-established is often slavishly adhered to, with little further thought about how it originated, why it is done or what it means. To justify it, the phrases "for the record" and "for protection" are often heard. Tests done only for these reasons not only are generally a waste of time and money but can also be quite misleading, and may give to the physician a false sense of security, or produce worry and concern over a potentially serious disorder when no disease actually exits."
-Diamond and Porter, NEJM 1958.

Testing of hemostasis is done for three reasons: to screen for coagulation disorders, to diagnose these disorders, and to monitor therapy. Tests of hemostasis and thrombosis are performed on nearly every patient in the hospital.

Bleeding Disorders

History

The bleeding history is the strongest predictor of bleeding risk with any procedure. It is essential that the bleeding history include more questions than just "are you a bleeder?" A good history for bleeding can be obtained in minutes by asking a few specific questions as outlined in chapter 3. Bleeding due to coagulation defects is unusual, recurrent, excessive, but rarely spectacular.

Specific Assays for Bleeding Disorders (Tables 2.1-2.3)

Prothrombin Time (PT-INR)

The PT-INR measures the amount of time it takes VIIa to form a complex with tissue factor and proceed to clot formation. The test is performed by adding tissue thromboplastin (tissue factor) to plasma. Prolongation of only the PT-INR most often indicates isolated factor VII deficiency. Combined prolongation of PT-INR and aPTT indicates either factor X, II, or V deficiency or multiple defects. However, depending on the reagent, occasionally mild (~50%) deficiency in factors V or X can present with only modest elevation of the PT-INR. The major clinical use of PT-INR is to monitor warfarin therapy. Since different laboratories use different reagents, the best way to monitor therapy is to use the International Normalized Ratio (INR).

The INR is a method of standardizing prothrombin times obtained from different laboratories. The INR is derived by dividing the patient's prothrombin time by the control and raising this to the International Sensitivity Index (ISI). The ISI is known for each prothrombin time laboratory reagent and it adjusts the prothrombin time for the differing sensitivities of reagents. Using the INR instead of the prothrombin time has resulted in more accurate monitoring of warfarin dosage. Many laboratories now only report the INR and not the prothrombin time.

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Table 2.1. Prothrombin time/INR

Plasma + Calcium + Tissue thromboplastin
TF+VIIa→Xa+V→IIa→CLOT

Table 2.2. Activated partial thromboplastin time

Plasma + Calcium + Kaolin + Phospholipids
Contact →XIa→IXa+VIII→Xa+Va→IIa→CLOT

Table 2.3. Interpretions of elavated PT-INR and/or aPTT

PT-INR Only Elevated
- Factor VII deficiency
  - – Congenital
  - – Acquired
    - - Vitamin K deficiency
    - - Liver disease
- Factor VII inhibitor
- Rarely in patients with modest decreases of factor V or X

PTT Only Elevated
- Contact, factors XI, IX, VIII deficiency
- Contact factor XI, IX, VIII specific factor inhibitor
- Heparin contamination
- Antiphospholipid antibodies

Both
- Factors X, V, or II deficiency
- Factor X, V, II inhibitor
- Improper anticoagulant ratio (Hematocrits >60 or <15)
- High doses of heparin (elevation of aPTT greater relative to PT-INR)
- Large warfarin effect (elevation of PT-INR greater relative to APTT)
- Low fibrinogen (<80 mg/dl)

Evaluation of an Elevated PT (INR)

If an elevated PT-INR is the only laboratory abnormality, this indicates a factor VII deficiency and usually confers no additional risk of bleeding since one needs only 5-10% of normal factor VII levels to support hemostasis. Congenital factor VII deficiency is very rare and presents with childhood bleeding. Heterozygotes for factor VII deficiency present with no bleeding but an elevated prothrombin time (INR 1.5-2.0).

The most common acquired etiology of an elevated PT-INR is vitamin K deficiency due to warfarin use or inadequate vitamin K intake. Liver disease is the next most common acquired cause. Since factor VII has the shortest half-life, its synthesis (and levels) will drop first with liver disease. In combined elevations of the PT-INR and aPTT the differential is either the rare factor V, X or II deficiency or multiple acquired defects such as those occurring with DIC. In very sick patients levels of factor VII often fall, causing a modest prolongation of the PT (INR up to 3.0).

Table 2.4. Four causes of elevated APTT and response to 50:50 mix

1. Factor deficiency—Corrects
2. Antiphospholipid antibodies—Does not fully correct
3. Factor inhibitors—May correct at time 0 but then prolongs
4. Heparin—Does not correct (usually obvious from history)

Activated Partial Thromboplastin Time (aPTT)

The aPTT is performed by adding an activator such as clay to plasma. The aPTT measures the speed of the contact pathway (XII, kallikrein, XI)→IXa+VIIIa→Xa+Va→IIa→CLOT.

In patients with elevated levels of factor VIII, the aPTT can be shortened due to increased efficiency of the coagulation reactions. This is seen in inflammatory states, uremia, patients on cyclosporine, and in pregnant women.

There are four etiologies to consider when the aPTT is elevated:

1. **Factor deficiency**. The aPTT does not rise until the plasma level of a single coagulation factor is below 30-40%. However, only mild decrements (60-70% range) in multiple factors will prolong the aPTT.
2. **Lupus inhibitors (antiphospholipid antibodies)**. Antiphospholipid antibodies (APLA) are antibodies that react with certain phospholipids in the body. They will also react with the phospholipid in the test reagent for the aPTT. Thus, they will artifactually prolong the aPTT. The presence of these antibodies may indicate, paradoxically, a higher risk of thrombosis and not bleeding. They may be as part of an autoimmune disease, found after infections, with intake of certain medicines, and can occur in low titers in up to 30% of the population.
3. **Factor inhibitors**. These are antibodies to coagulation factors such as factor VIII. These inhibitors are usually found in hemophiliacs, or may be acquired in the elderly, or after pregnancy. Presence of these inhibitors is usually associated with severe bleeding, often with large ecchymoses.
4. **Heparin**. Heparin, even minute amounts, can prolong the aPTT. This most often occurs when blood for the aPTT is drawn from catheter lines.

How to Tell 1-4 Apart

The simplest way to avoid heparin contamination is always to draw blood from peripheral sites. In addition the thrombin time (see below) will always be prolonged with heparin. The 50:50 mix will differentiate the rest (Table 2.4 and 2.5). The 50:50 mix is performed by making a mixture of the patient's plasma and normal pool plasma and performing aPTT on the mix. The mixture is incubated for a period of time (usually 60 or 120 minutes) and the aPTT's are performed at those times. Each of the three major different etiologies of an elevated aPTT (ideally) will provide different results in the 50:50 mix:

1. **Factor deficiency**. An initially elevated aPTT will correct to normal at time 0 and stay in the normal range on each of the time points. Since it takes only 30-40% of normal coagulation factors to normalize the aPTT, even with a complete lack of a factor, the mixing in of the normal pool will raise this level to 50% and normalize the aPTT.

Table 2.5. Examples of 50:50 mixes

1. Factor VIII deficiency
2. Antiphospholipid antibodies
3. Factor VIII inhibitor

Time	0	30	60	120
Normal (25-35 seconds)	30	32	33	34
Patient's	50	52	55	53
50:50-DEF (1)	30	32	33	34
50:50-APLA (2)	40	38	42	39
50:50-INHIB (3)	30	40	45	65

2. **APLA**. The aPTT does not correct to normal at time 0 or any time point. The aPTT may actually prolong further with addition of patient's plasma (Lupus cofactor effect). The crucial point is that the aPTT will not *fully* correct with the 50:50 mix.
3. **Factor inhibitors**. The aPTT may correct to normal at time 0 but then prolongs with further incubation. This demonstrates the importance of the incubation step in performing the 50:50 mixing test. Really strong inhibitors may prolong the 50:50 mix aPTT even at time 0, but the aPTT will be more prolonged with longer incubation.

Bleeding Time

Once a standard screening test, the bleeding time is now very controversial. It is best viewed as sensitive but not specific. If a patient has a normal bleeding time, then their risk of bleeding with a procedure is low. Unfortunately, a prolonged bleeding time does not reliably predict bleeding with a procedure. Measuring the bleeding time before procedures is not useful in otherwise asymptomatic patients who do not have a bleeding history. Prolongation of bleeding time can occur with platelet disorders, with von Willebrand disease, and with connective tissue defects. The bleeding time lacks diagnostic specificity as a screening test. It is best used in the evaluation of patients with a history suggestive of a bleeding disorder.

Platelet Function Analysis

Recently a number of laboratory platelet tests have been developed to improve on the bleeding time. The most popular of these tests is the PFA-100. Whole blood is used for this assay and is exposed to either collagen/ADP or collagen/epinephrine surrounding a small hole. The endpoint of the test is closure of this hole due to platelet aggregation. The test appears to be more sensitive than the bleeding time for congenital bleeding disorders but, like the bleeding time, it is not useful for mass screening of patients. The major advantages of the PFA-100 are that it is not as dependent on technical factors and is reproducible.

Specific Factor Assays

The standard method for measuring coagulation factors is by assaying their activity level. Many bleeding defects are due to abnormal factors and not absent ones. Furthermore, measuring activity levels is easier than directly measuring antigen levels.

The assays are performed by mixing the patient's plasma with sample plasma that is missing a specific coagulation factor. For example, if someone is factor VIII deficient and their plasma is mixed with a factor IX deficient plasma the clotting time will correct. If, however, the patient's plasma is mixed with a factor VIII deficient plasma, the clotting time will remain prolonged. To measure the exact level of factor deficiency, the clotting time with the deficient plasma is compared with a series of clotting times done with known factor levels. For example, if the plasma has a clotting time of 45 seconds, looking on a standard curve and note the clotting time for 10% factor VIII is 42 seconds and the time for 5% factor VIII is 47 seconds. By extrapolation the patient has only 7% factor VIII.

Tests for DIC (Disseminated Intravascular Coagulation)

Simply put, DIC is inappropriate activation of thrombin (IIa). As discussed in chapter 8, this leads to 1) conversion of fibrinogen to fibrin, 2) activation of platelets (and their consumption), 3) activation of factors V and VIII 4) activation of protein C (and degradation of factors Va and VIIIa), 5) activation of endothelial cells, and 6) activation of fibrinolysis.

There is no one test that will diagnosis DIC; one must match the test to the clinical situation.

Screening Tests

The PT-INR and aPTT are usually elevated in DIC with severe depletion of coagulation factors but may be normal or even shortened in chronic forms where increased coagulation factor synthesis can compensate for factor depletion. One can see a shortened aPTT in DIC for two reasons. In patients with severe DIC, a large amount of activated II and factor X is "bypassing" the contact pathway; aPTT's as short as 10 seconds have been seen in acute DIC. In chronic DIC the high levels of factor VIII leads to a shortened aPTT. The platelet count usually falls but may be normal in chronic DIC. Serum fibrinogen is low in DIC but again may be in the "normal" range in chronic DIC.

"Specific Tests" for DIC

These are a group of tests which allow one to deduce that abnormally high concentrations of IIa are present. (Table 2.6)

Ethanol Gel and Protamine Tests

Both of these tests detect circulating fibrin monomers. Circulating fibrin monomers are present when IIa acts on fibrinogen. Usually the monomers polymerize with the fibrin clot but when there is too much IIa, these monomers can circulate. Detection of circulating fibrin monomers means there is too much IIa and, *ergo*, DIC.

Fibrin Degradation Products (FDP)

When plasmin acts on the fibrin/fibrinogen molecule, it cleaves the molecule in specific places. Thus, FDP levels will be elevated in situations of increased fibrin/fibrinogen destruction (DIC, fibrinolysis). Fibrinogen degradation products result from destruction of circulating fibrinogen and fibrin breakdown products from a fibrin clot. High levels of FDP are seen also in dysfibrinogenemias. This is because in the first step of the test all the fibrinogen is clotted and then reagents are used to detect any left-over fragments. Since abnormal fibrinogen cannot clot, it will also be detected. This is one reason that elevated "FDPs" are often seen in liver disease.

Table 2.6. Specific tests for DIC

Protamine sulfate/ethanol gel: Detects circulating fibrin monomers (DIC)
FDP: Fibrin and fibrinogen degradation products
D-dimers: fibrin degradation products.

Table 2.7. The thrombin time

Add Thrombin to Plasma→CLOT

Elevated In:
1. Heparin use
2. DIC
3. Dysfibrinogenemia
4. Low fibrinogen levels
5. High fibrinogen levels
6. Uremia

D-Dimers

When fibrin monomers bond to form a thrombus, factor XIII acts to bind their "D" domains together. The resulting bond is resistant to plasmin; the degradation fragment is called the "*D-dimer.*" Elevated levels of D-dimer indicate that 1) thrombin has acted on fibrinogen to form a fibrin monomer that bonded to another fibrin monomer by factor XIII and 2) this clot was lysed by plasmin.

To summarize, since high levels of plasmin can destroy both fibrinogen and fibrin, clinicians need to distinguish between *fibrin* and *fibrinogen* degradation products. The difference between these two is that when a clot is formed, factor XIII stabilizes the clot by forming peptide bonds between the fibrin monomers. The distal end of the fibrinogen molecule is called the "D-domain." Plasmin cannot break the bond linking the adjacent two D-domains, which can then be detected by the fibrin degradation product test; i.e., the D-dimer assay.

Thrombin Time (Table 2.7)

This test is performed by adding thrombin to plasma. The added thrombin directly clots fibrinogen. The thrombin time is only affected by factors that interfere with thrombin or fibrinogen. The thrombin time is elevated in: 1) DIC (FDP's interfere with polymerization), 2) low fibrinogen levels, 3) dysfibrinogenemia, and 4) in the presence of heparin (very sensitive).

Reptilase Time

This is the same as thrombin time but is performed with a snake venom (*Bothrops atrox*) that cleaves fibrinogen and is insensitive to heparin. The reptilase time is elevated in the same conditions in which the thrombin time is elevated but the reptilase time is not affected by heparin. Thrombin time and reptilase time are most useful in the evaluation of dysfibrinogenemia.

Ecarin Time

The ecarin time is performed by using the snake venom from *Echis carinatus* (sawtooth viper). This venom directly activates prothrombin, leading to clot formation. It is inhibited by direct thrombin inhibitors and is useful for monitoring the antithrombin class of antithrombotic agents such as lepirudin and argatroban.

Fibrinogen Levels

Fibrinogen activity levels are assayed by using a modified thrombin time. The causes of a low fibrinogen level are:

- Liver disease
- Disseminated intravascular coagulation
- Dilution (i.e., massive transfusions)
- Dysfibrinogenemia

Thromboelastography (TEG)

TEG is a unique laboratory test that examines whole blood thrombus formation and lysis. TEG is performed by placing a 0.35 ml of whole blood into an oscillating container with a pin that measures the force of thrombus formation. TEG measures five parameters:

- r time: time from starting TEG until clot formation.
- K time: time between tracing going from 2 mm to 20 mm.
- Alpha angle: slope of tracing between r and K time.
- MA: greatest amplitude of TEG tracing.
- Whole blood lysis index: amplitude of tracing 60 minutes after MA.

Most modern TEG machines automatically calculate these parameters. In addition, some TEG have a heparinase container for use in patients on heparin. Currently the main use of TEG is with liver transplantation and cardiac surgery. TEG allows rapid point-of-care testing of coagulation and is particularly useful in assessing fibrinolysis.

Thrombotic Disorders

As with bleeding disorders, the history is important for evaluation of thrombotic disorders. Patients need to be quizzed not only about obvious thrombosis but also about episodes of leg swelling, shortness of breath, and diagnoses of "walking pneumonia." The family history is also crucial. Like bleeding disorders, hypercoagulable states are often heritable but with incomplete penetrance so one needs to be persistent in questioning.

Tests for Antiphospholipid Antibodies (APLA)

APLA's are important to detect because in certain patients they are associated with a syndrome that includes a hypercoagulable state, thrombocytopenia, fetal loss, dementia, strokes, Addison's disease, and skin rashes. There are two main tests for APLA's: testing for presence of antibodies to cardiolipin and the coagulation-based tests for APLA.

Coagulation-Based Tests

As noted above, APLA reacts with phospholipid. The phospholipids provide a surface where the coagulation reactions take place. The basis for all the coagulation-based tests is that antibodies on the phospholipid will prolong the coagulation reactions and thus the test time. Once an elevated aPTT is found, one must verify it by showing it does not fully correct with a 50:50 mix. To prove the inhibitor is dependent on phospholipids one then adds phospholipid derived from platelets or hexagonal phase phospholipids. APLA reacts strongly with these phospholipids, and addition of these will correct the coagulation tests by absorbing out the APLA.

To summarize, one screens for APLA with coagulation-based tests to see if any clotting times are prolonged. If a test result is elevated, then a 50:50 mix is done to ensure the elevation is not due to a specific factor deficiency. Then one uses a phospholipid source to correct the clotting time and verify the presence of APLA.

Specific Assays

aPTT: The routine aPTT only detects 30% of patients with APLA and are inadequate as a single test for APLA screening. One can increase sensitivity by using different aPTT reagents.

Dilute Russell viper venom time (dRVVT): This test is very sensitive to any interference with phospholipids and is very sensitive to APLA. It is performed by initiating the coagulation cascade with Russell Viper venom which directly activates factor X and is very sensitive to phospholipids.

Kaolin clotting time: This test uses no added phospholipid and is a sensitive test to detect APLA. However, it is technically demanding to do properly.

Platelet neutralization test: This test takes a coagulation reaction that is prolonged by plasma and does not correct with a 50:50 mix. Extracts of platelet phospholipids are added to the plasma and an aPTT is performed. The platelet phospholipid is very avid for APLA and "soaks up" the antiphospholipid antibody and corrects the aPTT. If the aPTT corrects with addition of platelets this is diagnostic for APLA.

Hexagonal phospholipid neutralization: This test is based on the same principle as the platelet neutralization test but it uses hexagonal phospholipid which is more specific for antiphospholipid antibodies. Current test kits that use hexagonal phospholipids also have added plasma and inhibitors of heparin. The additional reagents allow this assay for lupus inhibitors to be performed on anticoagulated patients.

Anticardiolipin antibodies (ACLA): This is an ELISA test for antibodies to cardiolipin. Therefore, it can be performed on plasma that has been anticoagulated. Tests results are reported in arbitrary units. Tests are also reported as specific isotype (IgG, IgA, IgM). It is still debated whether specific isotypes indicate specific diseases but most "secondary" (i.e., associated with infection) ACLA tend to be IgM subtypes.

Anti-beta2 glycoprotein antibodies: Although "APLA" are named for antibodies to phospholipids, the real targets are phospholipid-protein combinations. For anticardiolipin antibodies the protein target is beta$_2$-glycoprotein (B_2GP). It appears that anti-B_2GP antibodies may be more specific for pathogenic APLA, as they are usually negative in infection-associated APLA and other APLAs not associated with thrombosis. Currently anti-B_2GP testing is most useful in evaluation of the low-titer ACLA.

Approach to the patient suspected of having APLA: Unfortunately no single test can screen a patient for APLA. One must perform the entire panel on patients suspected of having APLA. The panel would include

- Anticardiolipin antibody
  - Anti-B2 glycoprotein for indeterminate results
- Texts for lupus inhibitor
  - Hexagonal phospholipid assay
  - Dilute Russell viper venom time
  - 50:50 mixing studies

Hypercoagulable States

There are several tests to detect inherited or acquired hypercoagulable states as outlined in Chapters 17 and 18. The best method is, again, to perform activity assays. Activity assays can be performed for the major inherited disorders including protein C, protein S, antithrombin III deficiencies and hereditary resistance to activated protein C. Since proteins C and S are vitamin K- dependent proteins, their levels will be falsely low in patients taking the vitamin K-blocking blood-thinner warfarin.

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CHAPTER 3

Bleeding Disorders: A General Approach

Patients with bleeding disorders may present in a variety of ways. Using the history and basic screening tests, one can narrow the differential considerably. Key questions to ask are (Table 3.1):

Is the Bleeding Real?

Patient perception of bleeding is not always useful in diagnosing a bleeding disorder. One should specify in detail the history of bleeding. The following questions are helpful in obtaining a bleeding history:

1. Have you ever had a nosebleed? How frequently do these occur? Has any required a trip to the hospital?
2. Have you ever had bleeding with dental work? Did it require stitching or packing due to the bleeding? Did it bleed the next day?
3. What surgeries have you undergone? Did any of them require transfusions? Did your surgeon comment on excessive bleeding?
4. What is the biggest bruise you ever had? How did it happen?
5. How long are your menstrual periods? Have you ever been so anemic you needed to be on iron replacement? Did you have excessive bleeding after childbirth or require a transfusion then?
6. Have you ever had bleeding when you urinated, from your stomach, or from your gastrointestinal track?
7. Do your gums bleed when you brush or floss your teeth?

Bleeding with coagulation disorders is excessive for the situation, prolonged, and recurrent. For example, a patient with hemophilia will bleed for several hours from a minor wound before a clot forms and then the bleeding may recur for days. Patients with mild bleeding disorders will manifest bleeding with dental extractions and surgeries. However, some patients with von Willebrand disease (due to the variability of the disease) may have had previous hemostatic challenges and not suffered significant bleeding.

Table 3.1. The key questions

1. Is the bleeding real?
2. Is it platelet type bleeding or coagulation defect bleeding?
3. Is it acquired or congenital?
4. What tests do I perform and how do I Interpret them?

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Is the Bleeding Due to Factor Deficiencies or Platelet Defects?

Patients with bleeding due to platelet defects (and von Willebrand disease) will manifest mainly mucocutaneous bleeding. They will have excessive bruising, gingival bleeding, and frequent nose bleeds. Patients with coagulation factor deficiencies will tend to have muscle and joint bleeds. Both groups of patients will bleed excessively from injuries and at the time of surgery.

Is It an Acquired or Inherited Disorder?

Patients with inherited bleeding disorders can present anytime from birth until old age. Patients with mild hemophilia or von Willebrand disease may not have worrisome bleeding until their first trauma or surgery. Therefore, the presence of an abnormal aPTT in an older patient should NOT be ignored because "they are too old to have hemophilia." Classic hemophilias A and B (factors VIII and IX deficiency) are sex linked so it is important to ask about bleeding in brothers, cousins and uncles. Von Willebrand disease is autosomal dominant but may have variable penetrance. Acquired bleeding disorders will often present suddenly with severe bleeding and newly abnormal coagulation tests. Often these patients have other illnesses, but autoimmune coagulation diseases can suddenly strike any previously healthy person.

What Tests Do I Need to Perform and How Do I Interpret Them?

A patient with a suggestive history of bleeding should have a PT-INR, aPTT, platelet count and bleeding time (or PFA-100) performed. The following patterns are most often seen (Table 3.2):

Elevated aPTT Only

Factor VIII, IX, XI deficiencies are associated with an increased aPTT and bleeding. Factor VIII and IX deficiency will present as classic "hemophilia." Factor XI deficiency has more variable bleeding tendencies and often is associated with post-surgical bleeding. Acquired factor inhibitors will present often with a sudden onset of bleeding. Factor XII and contact protein deficiencies do not have associated bleeding. Patients with lupus inhibitors rarely bleed. Some patients with APLA will have bleeding if they have associated prothrombin deficiency. The laboratory clue is that they will also have an elevated PT-INR.

Elevated PT-INR Only

Only an isolated factor VII deficiency will present with an elevated PT-INR. One only requires a factor VII level of 5-10% for hemostasis, so most modest elevations (less than an INR of 5) will not lead to bleeding.

Elevated PT-INR and aPTT

The rare factors X, V and II deficiencies have both an elevated PT-INR and aPTT. More common etiologies are multiple deficiencies due to liver disease, vitamin K deficiency or disseminated intravascular coagulation. Lupus inhibitors with associated anti-prothrombin antibodies can also present with both tests elevated.

Decreased Platelet Counts

See Chapter 7 for a discussion on thrombocytopenia.

Table 3.2. Most common test results and likely (not exhaustive!) diagnoses

- Elevated PT-INR only: Chronic liver disease, mild vitamin K deficiency
- Elevated aPTT only:
  - Not bleeding: Lupus inhibitor, factor XII deficiency
  - Bleeding: Heparin contamination (if drawn through catheter), factor VIII deficiency or inhibitor, factor IX deficiency
- Both PT-INR and aPTT elevated: Warfarin or heparin effect, severe liver disease, DIC
- Abnormal bleeding time: Aspirin, Cox-1 inhibitors, von Willebrand disease, platelet function defects, uremia, liver disease

Table 3.3. Additional tests to order in bleeding patients with normal screening tests

- Plasma fibrinogen
- Thrombin time
- Reptilase time
- Euglobulin clot lysis time
- Factor XIII level
- Plasminogen activator inhibitor-1 level
- Alpha$_2$-antiplasmin level

Increased Bleeding Time/PFA-100

This is seen either with von Willebrand disease or platelet function disorders. An elevated aPTT is seen only rarely in von Willebrand disease when the factor VIII level is below 30%. Patient who ingest aspirin or non-steroidal antiinflammatory agents may have a prolonged bleeding time. Prolonged bleeding times are routinely seen in liver and renal disease. The elevated bleeding times present in liver and renal disease patients are of little prognostic value for risk of bleeding.

Rare patients may have a normal PT-INR, aPTT, platelet count, and bleeding time but have a bleeding diathesis. In these patients one should check: (Table 3.3):

- Plasma fibrinogen to rule out dysfibrinogenemia.
- Euglobulin clot lysis time to rule-out fibrinolysis.
- Factor XIII level.
- Plasminogen activator inhibitor-1 level.
- Alpha$_2$ antiplasmin level.

CHAPTER 4

Hemophilia

Introduction

Hemophilias A (factor VIII deficiency, "classic hemophilia") and B (factor IX deficiency) are common bleeding disorders. Hemophilia A occurs in about 1:5,000 males, with hemophilia B occurring a fourth less frequently. Patients with severe disease require continuing care due to complications of bleeding. Patients with less severe disease will need factor VIII or IX replacement and special care at the time of trauma or surgery. Some patients with mild disease may not present until adulthood or will minimize any bleeding symptoms.

Pathophysiology and Classification

Normally, after initiation of coagulation, the tissue factor—VIIa complex activates factor IX. Factor IX, along with its co-factor VIII, then activates factor X. Patients with hemophilia bleed due to a lack of factor VIII or IX. Tissue factor-VIIa can directly activate factor X, but this reaction is soon quenched by formation of Tissue Factor Pathway Inhibitor (Fig. 4.1).

Hemophilia is arbitrarily classified as mild (>5% factor VIII or IX), moderate (1-5%) or severe (<1%). Mild patients often bleed only with severe trauma, surgery or dental procedures. Moderate patients bleed with minor trauma. Severe patients may have unprovoked bleeding. Although measurement of factor levels can help predict bleeding, many other conditions such as co-inheritance of factor V Leiden can influence the rate and severity of bleeding.

Symptoms

Severe deficiency in factor VIII or IX when untreated classically leads to bleeding in the joints, muscles and brain.

Untreated joint bleeds commonly lead to crippling arthritis and ultimately joint replacement in adulthood. Bleeds most commonly happen in the knee or elbow, but the ankle and shoulder can also be affected. Often one joint (the "target joint") will be affected out of proportion to other joints. The cycle of bleeding often starts with hemorrhage into the synovial space. This intrasynovial blood sets up an inflammatory reaction leading to pain, warmth, and swelling. This inflammatory reaction leads to hypertrophy of the synovium. The hypertrophied synovial tissue becomes boggy, vascular, and fragile leading to more bleeding that starts the cycle all over again. The synovial growth then leads to joint destruction and arthritis.

If the patient is a toddler, the sign of a joint bleed may be irritability and not moving the joint. Older children and adults will often feel a "tingling" in the joint, heralding the bleed. Patients with mild hemophilia may not appreciate that they are bleeding into a joint but may just complain about frequent "sprained" ankles.

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

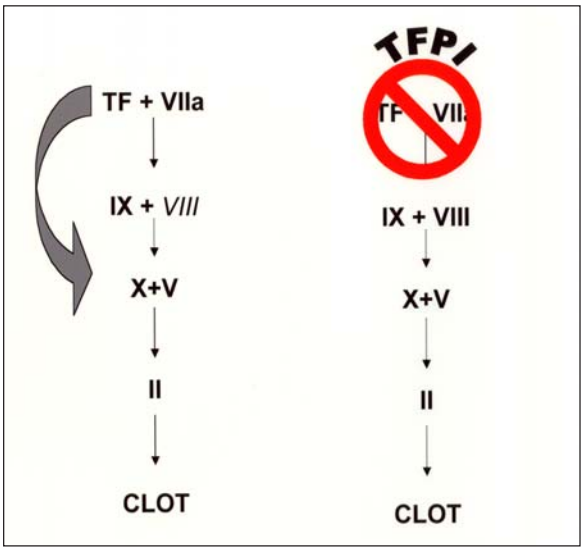

Fig. 4.1. Why Hemophiliacs bleed.

Due to the preexisting damage, hemophiliac joints are more prone to septic arthritis. Initial presentation of a septic joint can be the same as with a bleed. There can be mild warmth and severe pain but septic joints will not improve with factor therapy and will continue to worsen. Patients with *Staphylococcus aureus* infection will typically have high fevers and elevated white counts at presentation.

Bleeding can occur in any muscle group. Hemorrhage in the psoas muscle can be particularly devastating. Blood may track down the psoas muscle causing compression of the femoral nerve with resulting paralysis of the quadriceps muscle group. Patients present with severe groin pain and the hip held in flexion with lateral rotation. Muscle bleeds in any limb may result in a compartment syndrome.

Cerebral hemorrhage occurs in 2-8% of severely affected patients and is the leading cause of hemorrhagic death in hemophiliac patients. The bleeding may be due to minor trauma or may occur spontaneously. The classic presentation is the patient complaining of the worst headache of his life.

Diagnosis

Because both the factor VIII and IX gene is on the X chromosome, hemophilia is a sex-linked disease. Hemophilia should be considered in any male patient who presents with bleeding. Patients may have affected grandfathers, uncles, and cousins but not parents. Twenty to thirty percent of patients with hemophilia represent new mutations and will have a negative family history. Unlike hemophiliacs, patient with von Willebrand disease, the most common bleeding disorder, rarely have joint bleeds. Since it is autosomal dominant, patients with von Willebrand disease will usually have an affected parent or female relative.

Patients with mild hemophilia may not be diagnosed until adulthood, when an episode of trauma, dental extraction, or surgical- induced bleeding leads to the diag-

nosis. Past episodes of bleeding are minimized or not recognized as abnormal. Some mild hemophiliacs will have only mildly elevated aPTT and can go on to have severe bleeding if this laboratory abnormality is not further evaluated.

Once hemophilia is suspected, the diagnostic approach to hemophilia is straightforward. Patients with an elevated aPTT should have factor VIII levels assayed first; if normal, then factor IX levels should be assayed. Patients with normal factor VIII and IX levels should be screened for rarer bleeding disorders (Chapter 6).

Therapy

In theory the treatment of hemophilia is simple—replace the missing factor. Purified and recombinant factor replacement is available for both hemophilia A and B. (Table 4.1)

Hemophilia A (Factor VIII Deficiency)

A number of Factor VIII replacement products exist. These ranges from "medium purity products" to pure recombinant products. Since all products derived from plasma sources are treated to inactivate hepatitis and HIV viruses, "purity"

Table 4.1. Replacement products

Factor VIII
- **Low Purity (< 50 VIII units/mg protein)**
  - Cryoprecipitate
- **Intermediate Purity (1-10 VIII units/mg)**
  - Humate-P (Behringwerke, Aventis Behring)
  - Profilate-OSD (Alpha)
- **High Purity (50-1000 VIII units/mg)**
  - Alphanate SD (Alpha)
  - Koate-DVI (Bayer)
- **Very High Purity (3000 VIII units/mg)**
  - Plasma derived/monoclonal antibody purified
  - Antihemophilic factor-M (American Red Cross)
  - Hemofil-M (Baxter)
  - Monoclate-P (Centeon)
- **Recombinant**
  - Bioclate (Bayer)
  - Helixate (Bayer)
  - Kogenate (Bayer)
  - Recombinate (Baxter)

FactorIX
- **Low Purity ("Prothrombin Complex Concentrates") (< 50 IX units/mg)**
  - Bebulin VH (Immuno)
  - Konyne 80 (Bayer)
  - Profilnine SD (Alpha)
  - Proplex T (Baxter)
- **Higher Purity (> 160 units/mg)**
  - MonoNine (Aventis Behring)
  - Alphanine SD (Alpha)
  - Immunnine (Immuno)
- **Recombinant**
  - BeneFIX (Genetics Institute)

Table 4.2. Calculation of replacement doses of factors VIII and IX

Replacement Dose for Factor VIII

$$\frac{\text{(desired Factor VIII concentration—current level)*weight (kg)}}{2}$$

Replacement Dose for Patients with Mild (< 5BU) Factor VIII Inhibitor

40 units VIII/kg plus 20 units/kg per BU of inhibitor.

Replacement Dose for Factor IX

(desired Factor IX concentration—current level)*weight (kg)

Continuous Infusion of Products

Factor VIII: Bolus of 50 units/kg followed by a continuous infusion of 4-5 units/hour guided by levels.

Factor IX: load with 100 units/kg and then use a continuousinfusion of 4-5 units/hour guided by levels.

refers to the presence of other proteins. Currently the "medium" purity products are used to treat von Willebrand disease, not hemophilia. The highest purity products (monoclonal antibody or chromatographically isolated factor VIII) are derived from plasma, while the recombinant products are produced by cell culture. Since human albumin is used to stabilize these recombinant products, they are not completely free of plasma-derived proteins.

In theory, one unit/kg of factor VIII will raise the plasma factor VIII concentrations by 2% leading to the replacement formula (Table 4.2):

$$\frac{\text{(Desired Factor VIII concentration—current level) x weight (kg)}}{2}$$

In an emergency one can assume the current level is zero and use the formula: (desired level/2) times weight in kilograms.

Despite the specific formula, factor recovery differs among patients and tends to be less with higher purity products. Under times of surgical stress both the recovery and half-life will be lower. Therefore, for all but the simplest procedures, therapy should be guided by factor VIII levels. Infusions should be repeated every 8-12 hours to achieve the desired level. Another method that is useful for achieving stable levels of factor VIII is continuous infusion of the product. The infusion should start with a bolus of 50 units/kg and then a continuous infusion of factor VIII at 4-5 units/kg/hour with adjustments guided by factor levels.

In a patient who has received multiple infusions, the history may be used to guide treatment for simple bleeds. A "recovery" study should be conducted before major surgeries are performed. This requires the infusion of 1000 units of factor VIII and then measuring levels pre-infusion and 1, 6, and 24 hours later. This recovery study will allow for accurate assessment of the amount needed for factor VIII replacement.

Desmopressin can be useful for treatment of minor bleeds and for minor procedures in patients with mild disease. Patients with mild hemophilia will have a substantial rise in their factor VIII level with administration of desmopressin. The intravenous dose is 0.3 μg/kg infused over 30-45 minutes one half-hour before the procedure. The dose for nasal desmopressin (Stimate) is one nasal squirt in patients under 50 kilograms and two squirts (one for each nostril) in patients over 50 kilograms. Doses can be repeated every 12-24 hours although tachyphylaxis will occur due to depletion of factor VIII storage sites.

Therapy of Hemophilia B (Factor IX Deficiency)

Until recently, therapy of factor IX deficiency was hampered by the lack of pure concentrate. Patients were treated with "factor IX concentrates" derived by absorbing out from plasma all the vitamin K-dependent proteins. The final product contained not only factor IX but also factors II, VII, and X. Due to problems with purity and thrombogenicity these older products are reserved for use in patients with factor inhibitors (below) and are not used for hemophilia B.

Now there are highly purified factor IX concentrates and recombinant factor IX available. The dosing for the highly purified concentrate is:

(Desired Factor IX concentration—current level) x weight (kg)

When using recombinant factor IX the result should be multiplied by 1.2. Treatment with factor IX is more unpredictable than with factor VIII due to a more variable half-life of the infused factor IX. Infusions should be repeated every 12 - 24 hours to achieve the desired level. As with factor VIII infusions, peak and trough should be measured in patients undergoing extensive procedures. For a continuous infusions one should load with 100 units/kg and then use a continuous infusion of 4-5 units/hour guided by levels.

Guideline for Specific Bleeds (Table 4.3)

Joint bleeding responds to raising the factor VIII or IX levels to 50-60% acutely and every other day dosing to achieve a peak of 40% until the bleed resolves . Patients should initially rest the joint but then gradually try to use it to prevent freezing of the joint. A short course of multiple infusions to raise factor levels to 15-25% may be useful for treating repeated bleeds. Painful joints will also respond to a short course of prednisone (20-40 mg PO daily for 3-5 days) along with factor infusions once a septic joint is ruled out. Infusions should continue until the pain stops.

Most muscle bleeds respond to a target factor level of 80-100%. Large bleeds, or those affecting vital structures, will require more aggressive therapy (levels of 100%) or even drainage for limb- threatening bleeds. In patients with bleeding into limb compartments, close monitoring of neurologic function is essential and infusions should be continued until the swelling resolves. If there is impending development of a compartment syndrome, fasciotomy may be necessary to preserve limb function.

For patients with oral bleeding, adjunctive therapy with anti-fibrinolytic agents is useful. Either epsilon aminocaproic acid (EACA) or tranexamic acid can be used. The dose of EACA is 200 mg/kg (maximum 5 grams) oral bolus followed by 100 mg/kg (maximum 5 grams) every six hours. Tranexamic acid is an alternative antifibrinolytic agent that is dose 25 mg/kg orally every eight hours. Often only a single dose of concentrate is required when antifibrinolytic therapy is used.

Gastrointestinal bleeding should be treated with the initial goal of factor levels of 100% and thereafter a trough level of 30% should be achieved until the lesion has healed. Patients with hemophilia will often have an underlying lesion as the source of their bleeding. Therefore, aggressive evaluation of the gastrointestinal tract is necessary after a bleeding episode.

Patients with hemophilia not uncommonly develop hematuria. Rare episodes of painless hematuria do not require investigation. Frequent, excessive hematuria, especially associated with other symptoms such as pain, requires aggressive evaluation to ensure there is not an underlying lesion present. Again, a peak of 100% and a trough of 30% are required for initial control of the bleed. Hydration is an impor-

Table 4.3. Guidelines for factor replacement (modified from DiMichele d)

Site of Bleed	Hemostatic Level	Hemophilia A	Hemophilia B
Joint	80% Acutely then 40% qOD until resolved	40 units/kg initially and then 20 units/kg every other day until healed	80 units/kg initially and then 40 units/kg every other day or third day as needed
Muscle	40-50%	20-40 units/kg per day until healed	40-60 units/kg Then 20-30 every other day as needed
Oral	100%*	50 units/kg*	100 units/kg*
Nose	Initially 80-100%, then 30% until healing	40-50 units/kg, then 30-40 units per day	80-100 units/kg Then 35-40 units every day
Gastrointestinal	Initially 100%, then 50% until healing	50 units/kg then 30-40 units/kg per day	100 units/kg then 30-40 units every day
Genitourinary	Initially 100%, then 30% until healing	50 units/kg then 30-40 units/kg per day	100 units/kg then 30-40 units every day
Central Nervous System	Initially 100%, then 50-100% for 14 days	50 units/kg then 25 units/kg every 12 hours	100 units/kg then 50 units/kg every day
Surgery/Trauma	Initially 100%, then 80-100% until wound healing begins, then 30% until suture removed.	50 units/kg then 40-50 units every 12 hours adjusted according to healing	100 units/kg then 50 units every day adjusted according to healing

*Anitfibrinolytic agents are useful for oral bleeding.
Note: for severe or persistent minor bleeding factor levels should be followed

tant adjunct therapy. Antifibrinolytic therapy should not be used since this can lead to formation of insoluble thrombi in the ureters.

Severe hemophiliacs who suffer head trauma, even with no significant bruising or swelling, should receive aggressive factor therapy. Any hemophiliac patient with a severe headache or new neurological signs should immediately receive factor replacement (aiming for 100% levels) before proceeding to an imaging study. In older patients, 50% of bleeds occur without a history of trauma.

Surgery in the Patient with Hemophilia

Surgery in patients with hemophilia requires close monitoring of the patient's factor levels and the wound for any bleeding. Close cooperation among hematologist, surgeon, and anesthesiologist is required. Before any major procedure a recovery study should be done. One hour prior to surgery, the appropriate dose of factor should be administered to give a predicted level of 100-120% with a post-infusion level obtained. A factor level should be obtained in the recovery room and in the afternoon to guide the evening dose. The trough should not fall below 70% for at least the first 48 hours after surgery. The trough level is gradually tapered but should

Table 4.4. Therapy for inhibitors

Prothrombin Complex Concentrate
Dosing: 100 units/kg
Bebulin VH (Immuno)
Konyne 80 (Bayer)
Profilnine SD (Alpha)
Proplex T (Baxter)
Activated Prothrombin Complex Concentrate
Dosing: 75 units/kg
Autoplex (Baxter/Hyland)
FEIBA (Immuno)
Recombinant Activated VII
Dosing: 90 μg/kg every 2-3 hours
Novo-Seven (Norvo-Nordisk)

be kept above 30% until full healing has occurred. For joint replacement, patients should have their levels raised to 50-80% before each physical therapy session to allow full participation in rehabilitation. Continuous infusions of factors is very useful in management of surgery as it allows more consistency in factor levels.

Inhibitors

Patients with severe hemophilia A and less often hemophilia B can develop antibodies (inhibitors) to infused factors. This complication occurs in 20-30% of patients (with 10% persisting) with severe hemophilia A and in less than 5% of those with hemophilia B. An inhibitor should be suspected if the post-infusion factor levels are lower than predicted. A more common sign that an inhibitor has developed is when there is no rise in post-infusion factor levels.

Inhibitor levels are measured in "Bethesda units." One Bethesda unit is the amount of inhibitor that can neutralize 50% of factor VIII in a 50:50 mix with two hours incubation. Patents can have low (<5 BU), or high titer inhibitors. Patients can also be classified by the response of their inhibitor to factor infusion. Patients whose titers do not change with factor challenge are called "low responders." Patient who have large elevations in inhibitor titers after infusion of factor VIII are called "high responders."

In between exposures to factor VIII, inhibitor patients may develop low antibody titers that allow a "window" for use of factor VIII with severe hemorrhage. If the patient is exposed to factor VIII for trivial bleeding episodes and he is a high responder, the antibody titer will rise dramatically. This will limit therapeutic options if the patient has a severe bleed. Therefore, inhibitor patients should not be exposed to any factor VIII-containing product unless severe or life-threatening bleeding is present.

Therapy for patients with inhibitors can be challenging (Table 4.4). For low titer inhibitors (< 10 BU), especially in low responders, one can try to "overpower" the inhibitor with large doses of factor VIII. This can be successful in patients with very low (<5 BU) titers but often after several days the inhibitor will increase in strength and can no longer be neutralized. The target factor VIII level should be over 30-50%. One strategy (Kasper) is to give 40 units VIII/kg plus 20 units/kg per BU of inhibitor.

Factor VIII inhibitors tend to be partly species specific. Porcine factor VIII can function effectively as a cofactor for human factor IX. Therapy should be guided by levels in the same manner as with human factor VIII replacement. Since there is an

unpredictable degree of inhibitor cross-reactivity, one should check antiporcine factor VIII titers before therapy. Unfortunately, many patients will develop high titer antibodies to the porcine factor VIII. The initial dosing is 100-150 porcine VIII units/kg. Availability of porcine factor VIII is also a problem.

For minor bleeds patients can be treated with a prothrombin complex. This is a concentrate of vitamin K-dependent proteins (II, VII, IX and X) that is "contaminated" by activated factors. Concentrates that have been "activated" are also available. Infusion of concentrate can bypass the factor X activation step and promote hemostasis. The difficulty with the prothrombin complex is that it can lead to disseminated intravascular coagulation and thrombosis. Also some products are contaminated by factor VIII and may induce factor VIII inhibitors to rise. These prothrombin complex products can also be ineffective for major hemorrhage. The dosing of the prothrombin complex concentrate is 100 units/kg. The activated product dose is 75 units/kg. These doses can be repeated every 8 to 12 hours. There is no effective way to monitor the effect of the infusion. The clinical effectiveness of these products is due to the "contamination" with active coagulation factors and not the presence of factor IX. Therefore, the newer and purer factor IX concentrates are not useful for inhibitor patients.

Recombinant VIIa is becoming the therapy of choice for many inhibitor patients. The VIIa binds to any exposed tissue factor and can directly activate factor X, bypassing the factor IX-VIII step. The dose is 90 μg/kg given every 2-3 hours. One difficulty is the lack of monitoring. Three doses often suffice for joint bleeds while prolonged administration (up to 10-14 days) is required for major surgery or intercranial hemorrhage.

Theoretically in patients with a high titer of inhibitors, plasmapheresis can be performed to removed the antibody in an emergency. Given the difficulties of line placement and the time it takes to perform the procedure, plasmapheresis is only practical for situations such as planned necessary surgery.

With aggressive therapy patient with inhibitors can develop tolerance. This treatment requires daily high doses of factor VIII (50-200 U/kg), often supplemented with immunosuppression to drive down the titer of the antibody. Immune tolerance protocols are demanding for the patient and may take many months to years before the antibody disappears.

Suggested Reading

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CHAPTER 5

Von Willebrand Disease

Introduction

Von Willebrand disease (vWD) is the most common inherited bleeding disorder. It affects up to one percent of the population. Despite its relatively high prevalence, many features of the disease and its affected protein were only clarified recently. The exact molecular pathogenesis of the most common type of vWD is still unknown.

Pathogenesis and Classification

Von Willebrand factor (vWF) is crucial for the interaction of a platelet with damaged vasculature (Fig. 5.1). VWF circulates as a multimer that varies in molecular weight with the highest multimers weighing up to 20,000,000 daltons. The higher molecular weight forms are the most effective at supporting the interaction between platelets and damaged endothelium. When vWF binds to damaged vessels (usually to exposed collagen) this alters the protein, creating a binding site for the platelet receptor Gp Ib. Thus, vWF is the "glue" between the platelet and damaged vessels. VWF is also the carrier protein for factor VIII. Unless protected by vWF, factor VIII is labile in the plasma. VWD results from either a drop in vWF concentration or impaired function.

Given the complexity of vWF, it make sense that there are several forms of vWD (Table 5.1). The most common form of vWD is a reduction in protein concentration. This is know as vWD type 1. In the type 2 variants the vWF itself is abnormal. In type 2A the vWF concentration is not reduced but its function is impaired. This most often leads to loss of the high molecular weight multimers of vWF. Type 2B is a fascinating sub-type in which there is a "gain in function" mutation rendering the vWF capable of binding to Gp Ib even without collagen binding. Therefore the protein can bind to platelets even while circulating in the blood stream. This leads to clearance and reduction of the higher molecular weight forms. In addition there is often mild thrombocytopenia. Type 2M vWD have reduced function of vWF without obvious change in the size of multimers. Patients with type 3 vWD have a homozygous defect with no vWF circulating and no factor VIII. These patients will often present with severe bleeding including joint bleeds. Type Normandy (2N) is often mistaken for classic hemophilia. Here, the vWF is unable to bind factor VIII. This leads to low factor VIII levels but normal vWF levels. Unlike in classic hemophilia, the inheritance of Normandy type is autosomal dominant with men and women equally effected. Finally, in "platelet-type" or "pseudo" vWD it is the platelet receptor that has the "gain of function mutation" that reduces both the number of platelets and the number of high molecular weight multimers.

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

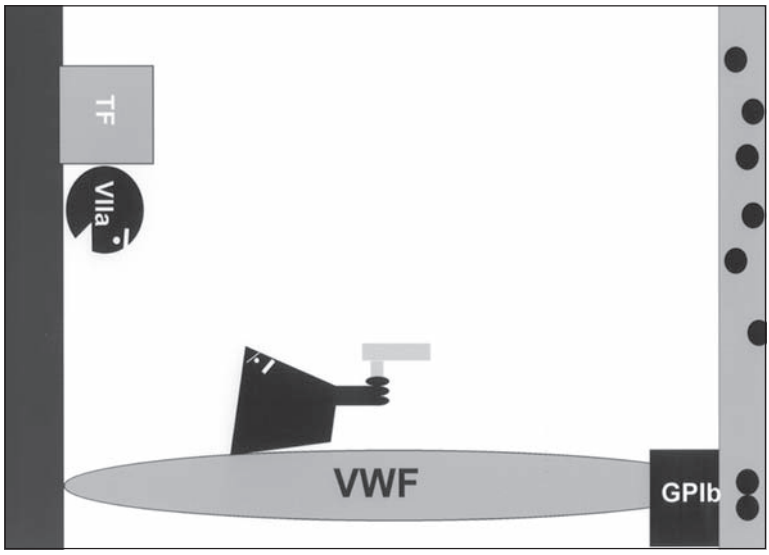

Fig. 5.1. The duel roles of von Willebrand's protein. VWF if both the carrier protein for factor VIII and binds platelets to damage vessel walls.

Table 5.1. Types of von Willebrand disease

Type 1:	Low levels of all proteins
Type 2:	Abnormal protein
Type 2A:	Abnormal protein leading to lower levels of high weight multimers
Type 2B:	Abnormal protein with increased binding to Gp Ib leading to lower levels of high weight multimers
Type 2N:	Lack of factor VIII binding site leading to low factor VIII levels
Type 2M:	Abnormal protein but normal multimer size
Type 3:	No von Willebrand or factor VIII present
Pseudo von Willebrand disease:	Abnormal Gp Ib leading to lower levels of high molecular weight multimers

Signs and Symptoms

Patients with vWD have "platelet-type" bleeding. They will often have severe nosebleeds and large bruises. Patients will come to clinical attention due to bleeding with minor surgeries such as tonsillectomies. Women can suffer from heavy menses. In fact, in some series up to one-third of women who present with the complaint of heavy menses will be found to have vWD. Unlike in classic hemophilia, joint bleeding is rare, except with the Type 3 patients. Patients often have a history of frequent

Table 5.2. Testing for von Willebrand disease

- Factor VIII level
- von Willebrand antigen
- Ristocetin cofactor activity
- Crossed immunoelectrophoresis

bleeding as a child but with lessening of symptoms as adulthood is reached. Unless specifically probed, patients often will not be aware of a significant bleeding history. Unexpected surgical bleeding can occur as the presenting problem in adulthood.

Testing

Testing for vWD can be challenging for several reasons. The plasma levels of protein in some patients can vary significantly from abnormally low to just in the lower range of normal. Stress, such as trauma, can transiently elevate levels. Finally, estrogens can greatly increase protein levels. Thus, knowing the patient's circumstances at the time of testing is important. Patients with histories suggesting platelet-type bleeding may require repeat testing to verify the diagnosis. Since women's levels of vWF vary with the menstrual cycle, menstruating women should have levels checked on day 5 through 7 of their cycle.

The bleeding time or PFA-100 can screen patients with a history of bleeding for vWD. However, in patients with variable protein levels the bleeding time can also be normal when the levels are in the normal range. Therefore, a normal bleeding time in a patient with a good history for platelet type bleeding does not eliminate the possibility of vWD.

Four tests are required to diagnose vWD (Table 5.2). The tests are:

- Factor VIII activity
- von Willebrand antigen (vWF:ag, old name VIII:ag)
- Ristocetin-cofactor activity (vWF R:Co)
- Crossed-immunoelectrophoresis

Factor VIII activity is proportional to the amount of vWF that is present and able to carry factor VIII. The level of vWF is a direct measurement of the protein. Ristocetin is an antibiotic withdrawn from the market due to thrombocytopenia. Ristocetin causes binding of vWF to platelets. The ristocetin cofactor activity (vWFR:Co) can serve as a rough measure of "von Willebrand activity." Newer assays can detect exposure of the active site that correlates with activity. Crossed-immunoelectrophoresis indicates the size distribution of von Willebrand protein and helps in sub-typing.

VWD should be suspected if factor VIII, vWF R:Co, or vWF:ag is below normal. Patients with mild reductions (50-60% levels) should have testing repeated. Since levels can vary, testing should be repeated if the initial panel is normal and the suspicion is high for vWD.

Type 1 patients have uniform reductions in all three tests and normal crossed-immunoelectrophoresis. If the vWF:Rco/vWF:ag ratio is below 0.7, one should consider a type 2 variant. If the FVIII/vWF:ag is below 0.7, one should consider hemophilia or vWD 2N.

In patients who lack the high-weight protein multimers, one has to decide if the condition is Type 2A, 2B, or pseudo-von vWD. The ristocetin-induced platelet aggregation test (RIPA) can help differentiate among these types. Type 2B and the

Table 5.3. Therapy of von Willebrand disease

Intravenous desmopressin 0.3 μg/kg can be repeated daily	
Intranasal desmopressin 300 μg (150 μg/nostril)	
Humate-P:	
Levels below 30%:	40-50 IU/kg followed by 20 IU/kg every 12 hours
Levels above 30%:	20-40 IU/kg every day
Type 1:	Desmopressin
Type 2A:	Desmopressin (only effective in 10%), Humate-P
Type 2B:	Humate-P
Type 2N:	Desmopressin
Type 2M:	Humate-P
Type 3:	Humate-P
Platelet-type:	Platelets+Humate-P, rVIIa

platelet type will show increased aggregation with addition of small amounts of ristocetin, while type 2A will have decreased activity. In addition, since many of these defects are limited to certain areas of the vWF, molecular studies can be helpful in determining the different type 2 subtypes.

VWD 2N should be suspected in women who have low factor VIII levels, when the inheritance appears to be autosomal dominant, or when the patient does not respond to Factor VIII concentrates. Diagnosis is established by performing vWF factor VIII binding study which is commercially available. The best diagnostic approach to 2M patients remains unsettled as there is still no consensus on how to perform and report testing.

Therapy

Several therapies are available for vWD (Table 5.3 and 5.4). Desmopressin leads to release of stored vWF from storage pools. In most type 1 patients desmopressin can lead to vWF levels adequate for hemostasis. Some type 2A patients will also respond. Desmopressin is usually avoided in type 2B and in platelet-type vWD. The fear is that such treatment will cause thrombocytopenia due to increased binding of vWF to the platelet which in turn can cause increased platelet aggregation and platelet clearance. The dose of desmopressin for types 1 and 2A is 0.3 μg/kg IV over 30 minutes. The rise in vWF occurs in 30 minutes and lasts for 4-6 hours. Tachyphylaxis can occur with repeated doses given every 24 hours. One side effect of desmopressin is retention of free water. In patients unable to control their water intake or in those receiving IV fluids, great care must be taken not to induce fatal hyponatremia.

Desmopressin is also available in a nasal spray which can be used before minor procedures. The dose for nasal desmopressin (Stimate) is one nasal squirt in patients under 50 kilograms and two squirts (one for each nostril) in patients over 50 kilograms. One must specify Stimate on the prescription as generic desmopressin is dosed inadequate for vWD.

Currently no specific concentrate is available for vWD. Humate-P is a factor VIII concentrate "contaminated" by vWF. Infusion of Humate-P is associated with shortening of the bleeding time and normalization of multimer patterns. Ideally the dosing of Humate-P is based on a patient's vWF R:Co. Humate-P is dosed either by factor VIII units or von Willebrand units with the conversion being 2 von Willebrand

Table 5.4. Procedures

Desmopressin responsive: Infuse 0.3 μg/kg to end 45 minute before procedure. May repeat every 24 hours. For major procedures follow factor VIII levels with plan to keep troughs over 80%.
Not desmopressin responsive: Humate-P to achieve peak over 120% and troughs of 80%:
Levels below 30%: 40-50 IU/kg followed by 20 IU/kg every 12 hours
Levels above 30%: 20-40 IU/kg every day

units equal to one factor VIII unit. Suggested dosing for major bleeding or surgery is an intravenous bolus of 40 IU/kg (all dosing in vWF units) followed by 20 IU/kg every 12 hours for three days and then 20 IU/kg every day for three to five days. For less severe patients 20-40 IU/kg every day may be effective.

It is unclear what laboratory test best predicts hemostatic effect with infusion. A practical way to follow therapy is to follow vWF R:Co and aim for peak levels of more than 100% and troughs of more than 40%. Obviously, the dosing should be adjusted depending on the factor levels. In patients with type 3 vWD or with very low factor VIII one should also measure factor VIII levels to ensure levels are adequate for hemostasis.

Cryoprecipitate contains a variable amount of vWF. Emergency dosing is 10 units every 12 hours until more specific factor is available.

Therapy by Type of von Willebrand Disease

Desmopressin is the mainstay of therapy for type 1 patients. For minor procedures it can be given once and can be repeated every day in patient undergoing major surgeries. One should follow vWF R:Co levels in patient undergoing major procedures to ensure adequate hemostasis. For dental work, addition of anti-fibrinolytic therapy such as amicar (100 mg/kg [maximum 5 grams] every 6 hours) or tranexamic acid (25 mg/kg TID) is useful.

Since 10% of type 2 patients respond to desmopressin, testing the patient for response is indicated. Type 2A patients who do respond to desmopressin tend not to respond in both absolute rise in factor and duration of response as well as Type 1 patients. For those patients who do not response to desmopressin, Humate-P is indicated.

Therapy of type 2B is Humate-P. Desmopressin may induce thrombocytopenia and worsen the bleeding diathesis.

Type 2N patents often respond to desmopressin. For non-responders or major surgery, Humate-P can be used.

Type 2M patients require Humate-P.

Therapy of type 3 patients requires Humate-P that also will supply the missing factor VIII. Many of these patients characteristically have “hemophiliac-type” bleeding and will require aggressive factor replacement. Ultimately many of these patents will require joint replacements.

Therapy of platelet-type vWD is challenging. If indicated, one must transfuse platelets and Humate-P together. The typical dose is 20 units of platelets followed by the appropriate dose of Humate-P. These patients represent a major management challenge and should only have procedures performed if absolutely necessary. In patients with refractory bleeding recombinant factor VIIa may be useful.

Pregnancy

Levels of vWF increase dramatically with pregnancy. The vast majority of patients with Type 1 vWD will normalize their levels with pregnancy and not require any therapy at the time of delivery. A von Willebrand panel at 32 weeks should be performed to ensure normal levels. Types other than type 1 may require therapy at the time of delivery. It is desirable to avoid desmopressin or factor replacement until after the cord is clamped. Patient with severe non-type 1 vWD may have excessive bleeding after delivery.

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CHAPTER 6

Other Inherited Bleeding Disorders

Platelet Defects

Introduction

Inherited platelet defects fall into two general categories: congenital defects in platelet function, and the inherited thrombocytopenic disorders. These syndromes cause varying degrees of platelet-type bleeding ranging from minor to severe.

Defective Platelet Function

Most patients with inherited disorders of platelet function have normal platelet counts. These patients present with signs of platelet-type bleeding such as nosebleeds and easy bruisability. These patients tend to be only mildly symptomatic and may have excessive bleeding with trauma and surgery. Although many patients on evaluation will be identified with specific defects of platelet aggregation, some patients will have a history of bleeding and a prolonged bleeding or PFA closure time but no identifiable defects.

Diagnosis is made by prolonged bleeding or PFA closure time in the presence of a suggestive history. Platelet aggregation studies can be useful in identifying specific defects such as Glanzmann's thrombasthenia or Bernard-Soulier syndrome.

No specific therapy exists for these disorders. Many patients respond to desmopressin, and any patients identified with a platelet bleeding disorder should receive a trial of desmopressin to see if the bleeding time shortens. Platelets should be given for severe bleeding. Data exists showing that recombinant factor VIIa is useful for patients with Glanzmann thrombasthenia and severe bleeding. All platelet products should be leucoreduced to prevent platelet alloimmunization.

Congenital Thrombocytopenia

Congenital thrombocytopenia can be associated with a number of diseases. Most patients have only mild thrombocytopenia in the 50,000-100,000 μL range with varying degrees of bleeding.

Diagnosis can be easy if the thrombocytopenia is part of a well-defined syndrome. Some patients with milder disorders may be labeled as having "mild immune thrombocytopenia." A careful review of the family history or review of family members' blood counts will reveal the inherited nature of the thrombocytopenia.

Patients with mild thrombocytopenia and no symptoms do not require any therapy. Symptomatic patients often response to desmopressin. Severely affected patients will require platelet transfusions.

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Table 6.1. Inherited defects of platelet function

Platelet function disorders with normal platelet numbers
- Collagen aggregation defects (inheritance pattern varies)
- Glanzmann thrombasthenia (AR)
- Dense body deficiency (autosomal recessive, AR)
- Secretion defect (varies)

Thrombocytopenia (large platelets)
- Alport's syndrome (AD)
- Autosomal dominant thrombocytopenia (AD)
- Bernard-Soulier (AR)
- Gray platelet syndrome (AD)
- May Hegglin anomaly (AD)
- Fechnter syndrome (AD)
- Montreal giant platelet syndrome (AD)

Thrombocytopenia (normal sized platelets)
- Chédiak-Higashi syndrome (AR)
- Thrombocytopenia with absent radius (TAR) (AR)
- Factor V Quebec (AD)

Thrombocytopenia (small platelets)
- Wiskott-Aldrich syndrome (X-Linked)

Named Platelet Disorders (Table 6.1)

Platelet Function Disorders with Normal Platelet Numbers

Collagen aggregation defects (inheritance pattern varies) patients have an isolated defect in aggregation to collagen.

Dense body deficiency (autosomal recessive, AR) platelets have no storage pools of ADP and serotonin. Patients have reduced platelet aggregation, especially in response to epinephrine and collagen. Electron microscopy will reveal the abnormal platelet structure.

Glanzmann thrombasthenia (AR) is a severe bleeding disorder in which the platelets lacks GP IIb/IIIa. Patient can have life-threatening bleeding from the time of birth. Platelet aggregation will demonstrate complete lack of aggregation to all agonists except ristocetin. In severely affected children, bone marrow transplantation can be curative.

Secretion defect (varies) encompasses a large number of disorders, including cyclooxygenase deficiency and defects in mobilizing calcium.

Thrombocytopenia (Large Platelets)

Alport's syndrome (AD) patients have a syndrome of nerve deafness and platelet bleeding and eventually develop renal failure. Platelets show abnormal aggregation to epinephrine, ADP and collagen.

Autosomal dominant thrombocytopenia (AD) is manifested by mild thrombocytopenia, larger (in some kindreds normal size) platelets and a mild bleeding diathesis. Some families have a markedly higher incidence of leukemias.

Bernard-Soulier (AR) is a defect in platelet GP Ib. Platelet aggregation shows decreased response to ristocetin.

Gray platelet syndrome (AD) platelets have no alpha granules, giving the platelet a characteristic gray appearance on the peripheral smear. Some patients develop myelofibrosis later in life. Platelet aggregation is abnormal to ADP, collagen, and thrombin.

May-Hegglin anomaly (AD) has normal platelet function but can be associated with increased bleeding in some patients. Rare patients have been reported to have prolonged bleeding times that have responded to an infusion of desmopressin. A diagnostic clue is Döhle bodies in the leukocytes.

Fechnter syndrome is the associated of thrombocytopenia, renal disease and nerve deafness with leukocyte inclusion bodies (the worst of Alports and May-Hegglin). Surprisingly the same genetic defect is responsible for May-Hegglin, Fechnter and Alports (MYH9). The reason for the variation in phenotype is unknown.

Montreal giant platelet syndrome (AD) has large platelets and mild bleeding. Platelets show abnormal aggregation to ristocetin, ADP, and collagen.

Thrombocytopenia (Normal Sized Platelets)

Chédiak-Higashi syndrome (AR) patients have albinism, recurrent infections, and inclusion bodies in the leukocytes and macrophages. Platelets show abnormal aggregation to epinephrine and collagen.

Thrombocytopenia with absent radius (TAR) (AR) patients have reduced number of bone marrow megakaryocytes. This syndrome may be a variant of Fanconi's anemia.

Factor V Quebec (AD) patients have delayed bleeding after injury. Platelet aggregation shows defects in aggregation to epinephrine and sometimes to ADP and collagen. Patients with have markedly elevated FDP but normal D-dimers on testing.

Thrombocytopenia (Small Platelets)

Wiskott-Aldrich syndrome (X-linked) patients have an immunodeficiency and severe eczema. Platelets show abnormal aggregation to ADP, collagen and thrombin.

Less Common Coagulation Disorders

Patients with classic hemophilia greatly outnumber these defects (Table 6.2). Common features are variable bleeding and autosomal inheritance. Most of these patients are treated with plasma infusions with some important exceptions.

Alpha$_2$ antiplasmin deficiency is rare, with patients showing umbilical stump bleeding, spontaneous joint and muscle bleeding, and excessive bleeding after trauma or surgery. The euglobulin clot lysis time may be normal, and diagnosis is made by measuring alpha$_2$ antiplasmin levels. One odd finding is a greater tendency for bleeding with increasing age. Therapy is with antifibrinolytic therapy.

Plasminogen activator inhibitor-1 deficiency presents in a similar fashion to alpha$_2$ antiplasmin deficiency. The euglobulin clot lysis time is more reliably shortened in these patients. Treatment is also with antifibrinolytic therapy.

Hypofibrinogenemic patients have a mild bleeding tendency. Total lack of fibrinogen (afibrinogenemia) has been reported with patients having a severe hemorrhagic disposition similar to classic hemophilia. Women have a higher risk of miscarriages and may benefit from prophylaxis. One unique feature is a propensity for spontaneous splenic rupture. Cryoprecipitate contains fibrinogen and is used for

Table 6.2. Rare factor deficiencies

Factor	Plasma Concentration	Level Needed for Hemostasis	Half-Life (hours)	Therapy
I	200-400 mg/dl	100 mg/dl	120	Cryoprecipitate
II	10 mg/dl	25%	50-80	Plasma
V	1 mg/dl	20-25%	24	Plasma, platelets
VII	0.05 mg/dl	15%	6	Plasma, rVIIA
VIII	0.01 mg/dl	100%	12	Concentrate, desmopressin
IX	0.3 mg/dl	100%	24	Concentrate
X	1 mg/dl	10-20%	25-60	Plasma, estrogens
XI	0.5 mg/dl	40-60%	40-80	Plasma
XIII	1-2 mg/dl	1-3%	150	Plasma
$Alpha_2$ antiplasmin	5-7 mg/dl	30% (?)	48	Antifibrinolytic agents
Plasminogen activator 1	0.005 mg/dl			Antifibrinolytic agents

replacement. Recommended dosage is one bag for every 5-7 kg of body weight. For prolonged replacement this initial dose can be followed by one bag of cryoprecipitate/15kg body weight daily. One should aim for trough levels of 80-100 mg/dl.

Dysfibrinogenemias have a variety of presentations ranging from asymptomatic (~50%), bleeding (~30%), or thrombosis (~20%). The PT-INR and aPTT are normal unless the fibrinogen levels is below 80 mg/dl. The thrombin time is usually prolonged but cases of dysfibrinogenemias exist where the thrombin time is shortened. Specific assays of fibrinogen activity will show low levels. In dysfibrinogenemia the fibrinogen antigen will be markedly elevated above activity levels and this discrepancy is the most valuable diagnostic clue. Therapy is with cryoprecipitate with dosage the same as for dysfibrinogemia.

Prothrombin deficiency has markedly elevated PT-INR and aPTT with the PT-INR elevated to a greater degree. Patients often bleed soon after birth but tend not to get hemarthrosis. Bleeding patients should be treated with plasma to achieve a prothrombin level above 25%. Given the long half-life of prothrombin, repeated transfusion may not be necessary for isolated bleeding episodes. For more aggressive therapy one can use prothrombin concentrates such as Konyne or Pro-filnine but these carry the risk of thrombosis.

Factor V deficiency patients have a mild to moderate bleeding disorder. Levels of factor V tend not be greatly predictive of bleeding. PT-INR and aPTT are prolonged. One should always obtain a factor VIII level, due to the rare syndrome of combined factor V and VIII deficiency. Bleeding patients are treated with plasma to achieve a level of 20-25%. Plasma is dosed as an initial dose of 20 ml/kg followed by 5 ml/kg every 12 hours to achieve a trough of 25%. Platelets also contain factor V and platelet transfusions may be useful in severe bleeding.

Factor VII deficiency is associated with severe bleeding including a high frequency of intracranial hemorrhage. Oddly, some patients with very low levels do not manifest bleeding, and excessive thrombosis has been reported. Patients have an isolated PT-INR elevation. Therapy is with plasma to achieve a level of 15%. Factor VII has a short half-life so plasma must be infused frequently. Recombinant VIIa dose at 25 μg/kg is also useful in these patients. In these patients one can simply monitor the PT-INR with a goal of achieving a normal value. Due to the short half-life of factor VIII frequent dosing may be necessary with plasma therapy.

Factor X deficiency is associated with severe bleeding including hemarthrosis and intracranial bleeding. The PT-INR and aPTT are prolonged. In bleeding patients 15 ml/kg of plasma should be infused to achieve a factor X level of 15-20%. If available, prothrombin complex concentrates (50 units/kg) contain factor X and may be useful for severe bleeding. Factor X levels do rise with estrogens and this may be useful in symptomatic women.

Factor XI deficiency has the most variation in bleeding tendencies of any factor deficiency and the bleeding tendency is not closely associated with factor XI levels. The disease is most commonly found in the Ashkenazi Jewish population. Patients who are symptomatic tend to have a mild-to-moderate bleeding disorder with an isolated elevated aPTT. Patient tend to bleed after surgical procedures and after dental surgery. Some heterozygotes may also exhibit mild bleeding. The family and personal history of bleeding tends to be more reliable than factor levels.

Patients can be treated with plasma but high levels (over 60%) are needed for hemostasis. Given that the half-life of factor XI is long, one can infuse a "loading dose" of 15 ml/kg plasma and then follow this with 3-6 ml/kg every 12 hours with goal levels being 45% for major surgery and 30% for minor procedures. With the volumes of plasma involved there is increased interest in the use of rVIIa, especially for trauma and major surgery. Some patients may also respond to desmopressin. For oral surgery antifibrinolytic agents are a useful adjunct.

Factor XII deficiency homozygotes have unmeasurable aPTT. This factor deficiency is not associated with any excessive bleeding. In fact, a mild tendency toward thrombosis has been claimed. Deficiency of prekallikrein and high-molecular weight kininogen present in a similar fashion with no excessive bleeding.

Factor XIII deficiency patients have a high incidence of intracranial hemorrhage and umbilical stump hemorrhage. Women may also suffer from frequent spontaneous abortions. Since factor XIII deficiency does not prolong the PT-INR or aPTT, specific testing must be done. Only low levels (1-3%) are needed for hemostasis, this can be accomplished by prophylactic weekly or biweekly cryoprecipitate infusions. Clinical trials are underway to test factor XIII concentrates.

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CHAPTER 7

Acquired Bleeding Disorders

The most common bleeding disorders in older patients are acquired bleeding disorders. The most frequent, immune thrombocytopenia, liver and renal disease, and DIC, are discussed in other chapters. This chapter reviews other causes of acquired bleeding disorders

Thrombocytopenia

Thrombocytopenia is a relatively common finding in hospitalized patients. For example, thrombocytopenia is very common in the critical care population, with platelet counts below 100,000/μL found in 25-38% of such patients. Finding the etiology is frustrating, as multiple factors may be producing the thrombocytopenia. A rational approach is to consider the differential from a mechanistic point of view. Thus defects in platelet production, increased platelet sequestration, or increased platelet destruction (immune or non-immune) can lead to thrombocytopenia.

The initial assessment of the patient should be rapid and should focus on whether the patient is bleeding or having thrombosis, the underlying disorder, current medications and (if available) past medical history.

The mode of presentation can be an important clue to the etiology of the thrombocytopenia . Patients who present only with severe thrombocytopenia and no other systemic signs or symptoms (outside of bleeding) and a normal blood smear most often will have either idiopathic or drug-induced immune thrombocytopenia.

If the patient is in the hospital, the reason for hospitalization is a very important indicator in the evaluation of thrombocytopenia (Table 7.1). Thrombocytopenia may be a diagnostic clue for infection, TTP, or a sign of sepsis in patients who present with multiorgan system failure. In hospitalized patients new onset thrombocytopenia may be a manifestation of heparin-induced thrombocytopenia (HIT), may be drug-induced, or might be a harbinger of sepsis.

The patient who presents with moderate thrombocytopenia (50-100,000/μL range) can be a diagnostic problem. Despite the modest degree of thrombocytopenia, counts in this range are commonly seen in TTP and HIT. Patients with hypersplenism will have counts in this range. Often the non-specific thrombocytopenia that occurs in post-surgical and critically ill patients will also be in this range. It is frequently difficult to specifically identify the etiology for modest thrombocytopenia.

Diagnostic Approach (Table 7.2)

Medication is a common cause of thrombocytopenia. Patients should be carefully questioned about over-the-counter medicine or "herbal" remedies. Hospitalized patients need their medication sheets reviewed with all the medicines the patient has received noted.

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Table 7.1. Diagnostic clues to acquired thrombocytopenia

Clinical Setting	Differential Diagnosis
Cardiac surgery	Cardiopulmonary bypass, HIT, dilutional thrombocytopenia
Interventional cardiac procedure	Abciximab or other IIb/IIIa blockers, HIT
Sepsis syndrome	DIC, ehrlichiosis, sepsis hemophagocytosis syndrome, drug-induced, misdiagnosed TTP, mechanical ventilation, pulmonary artery catheters
Pulmonary failure	DIC, Hantavirus pulmonary syndrome, mechanical ventilation, pulmonary artery catheters
Mental status changes/seizures	TTP, ehrlichiosis
Renal failure	TTP, dengue , HIT, DIC
Cardiac failure	HIT, drug-induced, pulmonary artery catheter
Post-surgery	Dilutional, drug-induced, HIT
Acute liver failure	Splenic sequestration, HIT, drug-induced, DIC

Table 7.2. Initial approach to thrombocytopenia

1. Obtain detailed history—especially any and all drug exposure
2. Assess for lymphadenopathy and hepatosplenomegaly
3. Review blood smear
4. Check liver function and renal function
5. Check LDH

Examination of the blood smear can quickly reveal whether pseudo-thrombocytopenia is present and verify the degree of thrombocytopenia. The smear should be carefully reviewed for presence of schistocytes. An evaluation for DIC should be performed. Laboratory assessment of liver and renal function should also be reviewed. A markedly elevated level of LDH out of proportion to other liver function abnormalities is often seen in TTP and hantavirus pulmonary syndrome. In TTP, fractionation of the LDH reveals elevation of all isoenzymes consistent with multi-organ damage. If there is any suspicion of HIT, a HIT assay should be immediately obtained.

Etiologies of Thrombocytopenia (Table 7.3)

Decreased Production

So-called "acquired amegakaryocytic thrombocytopenia" is relatively rare. Most marrow disorders that lead to thrombocytopenia will cause other cell lines to be affected. The leading cause of isolated thrombocytopenia due to marrow problems is heavy (more than one fifth/day) use of alcohol that leads to a megakaryocytic maturation defect. Clinically the platelets are small (MPV low). The count remains depressed for 3-5 days after alcohol is stopped but then rapidly rises with a "rebound" thrombocytosis. Thiazides and carbamazepine may also be associated with

Table 7.3. Differential diagnosis of isolated thrombocytopenia

Production Defects
- Amegakaryocytic thrombocytopenia
- Carbamazepine
- Alcohol

Sequestration
- Immune destruction
  - Idiopathic
  - Drug-induced
  - HIV
  - Sepsis
  - Post-transfusion purpura
  - Heparin-induced thrombocytopenia
- Non-immune destruction
  - Thrombotic microangiopathies
  - Microangiopathic hemolytic anemia
  - DIC

reduced platelet production. Late-stage HIV patients may have prolonged thrombocytopenia with pyrimethamine and other medicines.

Rare patients with autoimmune amegakaryocytic thrombocytopenia may present with severe thrombocytopenia but do not respond to steroids or immunoglobulin. On marrow biopsy they have diminished to absent megakaryocytes. The etiology is due to suppressor T-cells repressing platelet production. Therapy is with cyclosporine or anti-thymocyte globulin.

In elderly patients, mild thrombocytopenia may be the first indicator of a myelodysplastic syndrome. Patients with myelodysplasia usually have an elevated MCV even if anemia is absent.

Small platelets are a diagnostic clue to marrow production defects. A history of alcohol or carbamazepine use is also helpful to establish the diagnosis. Often bone marrow examination is required to document the reduction in megakaryocyte number or to search for evidence of myelodysplasia. If available, the platelet reticulocyte count may be helpful if it is low.

Sequestration

Splenomegaly due to any cause can lead to thrombocytopenia. Usually the platelet count is above 50,000/μL. The splenomegaly from increased venous pressures seen with congestive heart failure and respiratory failure may account for the mild thrombocytopenia seen in these disorders. Although the splenomegaly seen with liver disease is often blamed for a concomitant thrombocytopenia, most of the time this is due to lack of thrombopoietin synthesis or to immune destruction.

Increased Destruction-Immune

Immune destruction is the most common cause of thrombocytopenia. Often these patients will have low platelet counts (<20,000/μL) but large platelets. Contrary to popular belief, these patients will respond to platelet transfusion but the half-life of the transfused platelet is dramatically shortened (see below). Causes include:

Immune thrombocytopenia (ITP): Discussed at length in Chapter 11. ITP is a classic autoimmune disorder of young women. Usually it presents in an otherwise healthy person who notices the onset of increased bruising and petechiae. ITP is a diagnosis of exclusion. Treatment is evolving but initial therapy is steroids, with splenectomy for steroid failures. Severe thrombocytopenia with bleeding can be treated with immunoglobulin or anti-D (WinRho).

Sepsis: An almost universal finding in patients with sepsis syndrome is thrombocytopenia. Classically this has been ascribed to DIC or non-specific immune-mediated platelet destruction. Recent reports suggest that one mechanism is cytokine driven hemophagocytosis of platelets. The patients with hemophagocytosis had higher rates of multiple organ system failure and higher mortality rates. Inflammatory cytokines, especially M-CSF, are thought responsible for inducing the hemophagocytosis. Since there is no specific therapy for the thrombocytopenia, therapy is supportive.

Two recently "discovered" infectious agents, Ehrlichia and Hantavirus, are associated with multisystem illness and thrombocytopenia. Both human granulocytic Ehrlichia and human monocytic Ehrlichia present with moderate thrombocytopenia and lymphopenia. Review of the peripheral smear in Ehrlichia may reveal the organism in the neutrophils or monocytes. Hantavirus presents with respiratory failure and thrombocytopenia. The findings of hemoconcentration, thrombocytopenia, left-shifted white blood counts and greater than 10% circulating immunoblasts is almost diagnostic of Hantavirus in the clinical setting of respirator failure.

Drugs: Many of the drugs used in modern medicine have been associated with thrombocytopenia (Table 7.4). The most common drugs implicated in thrombocytopenia include heparin, histamine-2 blockers, antibiotics (sulfa drugs, beta-lactams), quinidine, and non-steroidal antiinflammatory agents. However, the list of drugs implicated in drug-induced thrombocytopenia is extensive, and any drug started within the last three months must be considered suspect.

Drug-induced thrombocytopenia is severe and sudden in onset. Usually the thrombocytopenia resolves when the drug is cleared from the body. Quinidine thrombocytopenia is associated with an HUS-like syndrome as described in Chapter 12.

Therapy consists of stopping the drugs. Patients with very low platelet counts will respond to steroids and immunoglobulin infusions.

Ticlopidine has been both associated with thrombocytopenia and a TTP-like syndrome. Since ticlopidine is often used for neurological indications, patient may be misdiagnosed as having further ischemia and definitive therapy is delayed. Mortality is substantial even with aggressive therapy.

Severe thrombocytopenia has been reported in 0.5-2% of patients receiving other specific GP IIb/IIIa inhibitors. The mechanism of thrombocytopenia is unknown but is speculated to be related to conformational changes in GP IIb/IIIa induced by binding of the inhibitors. Experience with abciximab has shown that infusion of immune globulin is not helpful. Platelet transfusions result in a prompt rise in platelet count until the drug is cleared from the patient.

Post-transfusion purpura: Patients with this mysterious disease will have the explosive onset of severe thrombocytopenia one to two weeks after receiving blood products. PTP occurs in patients who lack common platelet antigens such as PL_{A1}. For unknown reasons, exposure of the antigens from the transfusion leads to rapid destruction of the patient's own platelets. Unlike most immune thrombocytopenias, bleeding may be severe in PTP. The diagnostic clue is thrombocytopenia in a patient

Table 7.4. Most common drugs implicated in drug-induced thrombocytopenia

Abciximab	Morphine
Acetaminophen	Nonsteroidal anti-inflammatory agents
Allopurinol	Penicillamine
Amiodarone	Pentamidine
Amrinone	Phenytoin
Aspirin	Procainamide
Beta-lactam antibiotics	Prochlorperazine
Carbamazepine	Promethazine
Cimetidine	Quinidine
Codeine	Quinine
Danazol	Ranitidine
Diazepam	Rifampin
Digitoxin	Spironolactone
Digoxin	Sulfasalazine
Diltiazem	Sulfonylureas
Erythromycin	Tetracycline
Furosemide	Thioguanine
Gentamicin	Ticlopidine
Heparin	Tricyclic antidepressants
Hydrochlorothiazide	Trimethoprim-sulfamethoxazole
Interferon	Valproic acid
Lidocaine	Vancomycin
Meperidine	

who has recently received a red cell or platelet blood product. Treatment consists of steroids. Immunoglobulin is useful in severe cases. Rare patients may require plasmapheresis. The patient's thrombocytopenia will resolve in a few months. If patients with a history of PTP require further transfusions the red cells should be washed and only PL_{A1} negative platelets should be given.

Heparin-induced thrombocytopenia (HIT): Heparin can induce a unique form of immune thrombocytopenia. Unfortunately, some of these patients will then develop severe thrombosis. HIT is discussed in more detail in Chapter 22.

Increased Destruction-Non-Immune DIC

Discussed in Chapter 8.

Thrombotic Microangiopathies

Discussed in Chapter 12.

Dysfunctional Platelets

Subtle testing of platelet function has revealed that acquired abnormalities in function are extremely common but the clinical significance of these abnormalities is controversial. Of the many agents and diseases which result in impaired platelet performance, only the few reviewed below appear to be of clinical significance.

Drugs: Multiple drugs have been shown to inhibit platelet function but clinical bleeding has only been associated with a few. Aspirin is the agent shown to be associated with a higher risk of bleeding in clinical trials. Ketorolac (toradol) has also been associated with significant clinical bleeding. This is especially true with combined use of ketorolac and heparin.

Acquired platelet dysfunction was first seen with carbenicillin therapy but has been reported with multiple antibiotics, especially early anti-pseudomonas penicillins. Infusions of therapeutic doses of ticarcillin and carbenicillin into normal volunteers will reproducibly raise the bleeding time by the third or fourth day of drug administration. In some patients this prolongation of the bleeding time will persist for up to two weeks. The newer anti-pseudomonal antibiotics do not appear to have significant antiplatelet effects.

Myeloma: Increased bleeding times indicative of platelet dysfunction have been described in patients suffering from myeloma. Abnormal platelet function including decreased aggregation, adhesion and procoagulant activity has been described. This may be due to the abnormal protein coating the platelet. A severe and potentially fatal bleeding diathesis due to a paraprotein with affinity for Gp IIb/IIIa has been reported. These platelet function defects decline with treatment of the myeloma.

Cardiopulmonary bypass. As discussed in chapter 10, the complex milieu of cardiopulmonary bypass may cause multiple and profound changes at all levels of hemostasis. Along with thrombocytopenia some patients will have profound platelet dysfunction. Patients with post-pump thrombocytopenia may require multiple platelet transfusions to stop microvascular bleeding and may require raising the platelet count above 100,000/μL to compensate for the platelet function defect.

Diagnosis and therapy: Classically patients with inhibition of platelet function will have "platelet type" bleeding: bruising, diffuse mucosal oozing, and epistaxis. The diagnosis of platelet inhibition is a clinical one based on the patient's underlying illnesses and the medications that they are receiving. The bleeding time or PFA 100 time is only modestly useful. A normal bleeding time rules out platelet dysfunction as a cause of bleeding and a prolonged one is suggestive of a platelet defect. However, an abnormal bleeding time has *NEVER* been shown to be predictive of bleeding in any situation. The clinical history of prior bleeding is a better predictor of future hemorrhagic complications.

Appropriate treatment of severe bleeding believed due to abnormal platelet function is platelet transfusion. Desmopressin may augment platelet function in a number of disorders. However, desmopressin has been associated with thrombosis in older patients and should be used cautiously. Raising the hematocrit to more than 30% by transfusion or by use of erythropoietin will also improve hemostasis in uremia and perhaps in other disorders. Cryoprecipitate will shorten the bleeding time in uremia and liver failure.

Acquired Coagulation Factor Deficiency

Acquired defects of hemostasis may first present with either prolongation of routine coagulation laboratory values or with a serious bleeding diathesis. Frequently DIC and liver disease present with both PT and aPTT elevated. If there is no evidence of either disorder then further testing is needed. A 50:50 mix that corrects establishes the presence of factor deficiency. One that does not correct (even with added phospholipids) suggests a specific factor inhibitor.

The first step in evaluation is to obtain a prothrombin time (PT) and an activated partial thromboplastin time (aPTT). One should ensure the sample is obtained from a peripheral vein. Samples drawn through heparin-locked catheters, even with elaborate manipulation to prevent contamination, can result in falsely elevated results as discussed in Chapter 2. Three patterns of defects can be seen

(Table 2.4). Isolated elevations of the PT are indicative of an isolated factor VII deficiency. Isolated elevations of the aPTT are typically due to heparin contamination, lupus inhibitors, isolated defects of VIII, IX, XI, or the contact pathway. Mixing studies can provide information to narrow the list of possible diagnoses. Prolongation of both the PT and aPTT suggests multiple defects or deficiency of factors II, V, or X. Marked prolongation of the PT and aPTT can also be seen with low levels of fibrinogen (< 50 mg/dl).

Patients with hematocrits of greater than 60% may have spurious elevations of the PT and aPTT due to improper plasma:anticoagulant ratio in the sample tube. Further coagulation tests are ordered based on the PT and aPTT to define the defect better if the reason for the coagulation deficiency is not apparent by the history (i.e., severe liver disease).

Vitamin K Deficiency

Vitamin K is critical in the synthesis of coagulation factors II, VI, IX, X, protein C, protein S and protein Z. Patients obtain vitamin K from food sources and from metabolism of intestinal flora. Vitamin K is used as a cofactor in gammacarboxylation of the vitamin K-dependent proteins. The gammacarboxylation involves oxidation of vitamin K. Vitamin K is recycled in a step blocked by warfarin. Despite being a fat soluble vitamin, body stores of vitamin K are low and the daily requirement is 1 μg/kg/day.

Vitamin K deficiency can present dramatically. Once the body stores of vitamin K are depleted, production of the vitamin K-dependent proteins ceases and the INR will increase rapidly to extreme levels. This can be seen in patients with poor nutrition who have a mildly prolonged INR going into surgery but several days post-operatively have an INR of 50.

The diagnosis is suspected when there is a history of prolonged antibiotic use or malnourishment. One must also suspect vitamin K deficiency in a previously healthy patient who presents with an elevated INR that corrects with 50:50 mix. This is a common presentation of accidental or surreptitious warfarin or rat poison ingestion.

Treatment of vitamin K deficiency is by replacement of vitamin K. Most patients will respond rapidly to 10 milligrams orally. For a more rapid response, 5-10 mg may be given more than 15 minutes intravenously over at least 60 minutes. However, anaphylaxis has been reported with rapid infusion of vitamin K. Alternatively, plasma can be used for the bleeding patient. At least 3-4 units (15ml/kg) of plasma may be needed until the administered vitamin K takes effect. For life-threatening bleeding 40ug/kg of rVIIa can be given.

Antibiotics

Antibiotics can affect vitamin K metabolism in two ways. Most antibiotics with activity against anaerobes can sterilize the gut, eliminating microbial production of vitamin K. Certain cephalosporins that contain the N-methylthiotetrazole (NMTT) group can inhibit vitamin K epoxide reductase. This prevents the normal recycling of vitamin K. The most commonly implicated antibiotics are cefamandole, cefoperazone, cefotetan, cefmenoxime and cefmetazole. NMTT is released from the antibiotic and circulated with a half-life of 24 - 36 hours. The NMTT metabolite can accumulate in patients with renal failure. The use of prophylactic vitamin K (10 mg orally or intravenously/week) with these antibiotics has dramatically reduced

the incidence of vitamin K deficiency. Prophylactic vitamin K should be considered for every patient on these antibiotics.

Malnutrition

Since vitamin K stores are labile, patients with poor nutritional status are liable to become vitamin K-deficient. This is especially true if a patient has biliary problems or is on drugs that interfere with vitamin K metabolism. Aggressive use of nutritional supplements and parental nutrition has greatly reduced malnutrition-related vitamin K deficiency.

Rat Poison

Warfarin used to be the rodenticide in commercially available rat poisons. Certain rats (by anecdote from New York City) became resistant to warfarin. Now rat poison contains brodifacoum as the main rodenticide. Brodifacoum binds and irreversibly inhibits vitamin K recycling. Furthermore, it is highly fat soluble and has a long half-life. Patients who ingest rat poison present with an elevated PT-INR that is only transiently responsive to fresh frozen plasma or to small doses of vitamin K. Diagnosis is established by measuring brodifacoum levels. High doses of vitamin K, 25-50 mg three times per day, may be required for months to treat brodifacoum ingestion.

Specific Acquired Factor Deficiencies

Alpha$_2$ antiplasmin deficiency most commonly occurs in DIC and acute promyelocytic leukemia. As discussed in chapter 27, rare patients with excessive bleeding and low levels of alpha$_2$ antiplasmin may benefit from antifibrinolytic therapy. Rare cases of acquired alpha$_2$ antiplasmin deficiency associated with severe bleeding have been reported in amyloidosis.

Plasminogen activator inhibitor-1 deficiency has infrequently been reported in amyloidoses.

Hypofibrinogenemia is most commonly seen in liver diseases, following thrombolytic therapy, in dilutional coagulopathies from massive transfusions, and in severe DIC. Patients commonly exhibit bleeding with fibrinogen levels lower than 100 mg/dl. Since the formation of the fibrin clot is the endpoint of the PT and PTT, patients with low fibrinogen levels will have artifactually elevated PT and aPTTs. Therapy is with cryoprecipitate with an expected increase in plasma fibrinogen of at least 100 mg/dl after 10 bags.

Dysfibrinogenemias are most often seen in liver disease. Patients with hepatoma may also have dysfibrinogenemia. It is assumed that the liver dysfunction results in abnormal glycosylation of the fibrinogen which results in a dysfunctional molecule. The presence of an abnormal fibrinogen is established by an abnormal thrombin time, elevated levels of FDP's with normal D-dimers, and a discrepancy between fibrinogen activity and antigen. Most patients do not require specific therapy.

Prothrombin deficiency occurs in two clinical situations, antiphospholipid antibody disease and with topical thrombin therapy (discussed in detail below under factor V deficiency).

Approximately 10% of patients with lupus inhibitors will have antibodies that react with prothrombin. The antibodies do not react with the active site but lead to increased consumption of the molecule. Rarely this may result in bleeding.

Patients with antiphospholipid antibodies may have elevated prothrombin times for two reasons. One is that antiphospholipid antibody cross-reacts with the prothrombin time. The other cause is due to anti-prothrombin antibodies. The 50:50 mix will only correct with the antiprothrombin antibodies. These antibodies are not inhibitors but lead to increased degradation and factor deficiency.

Therapy of anti-prothrombin antibodies is with steroids. A reasonable dose is prednisone 60 mg every day. Prothrombin can be provided by factor infusions but the half-life will be short due to increased consumption. Most patients respond promptly to steroids.

Factor V deficiency. Factor V inhibitors are frequently seen in patients after the use of topical thrombin. Several weeks after surgery the patient will develop antibodies to bovine thrombin. Many patients will also develop an antibody to the bovine factor V that is often also present in the bovine thrombin. This antibody will readily cross-react with human factor V. Rarely antibodies to human thrombin will also be seen.

Patients may present with severe bleeding or with an inhibitor detected on routine laboratory screening. The thrombin time is always prolonged as it is performed using bovine thrombin. If factor V antibodies are present, the PT and aPTT will also be prolonged and behave as an inhibitor in the 50:50 mix. Due to presence of the inhibitor, Factor V levels are reduced.

Many patients with factor V antibody do not bleed. One reason may be that platelet factor V, inside the platelet alpha granule, is protected from circulating antibodies. For the bleeding patient, therapy with plasma and platelets may be used. The antibodies will disappear in several weeks.

Acquired factor V deficiency has also been reported with myeloproliferative syndromes. These patients demonstrate a reduced half-life of factor V with plasma transfusion.

Factor VII deficiency is usually seen with vitamin K deficiency or with liver disease. Factor VII has the shortest half-life of the vitamin K-dependent proteins and its levels fall first as vitamin K supplies fall. Rare inhibitors of factor VII have been reported. For unclear reasons, levels of factor VII fall in severe illness leading to prolongation of the INR.

Factor VIII deficiency due to specific factor antibodies is the most frequent acquired factor deficiency. This can be seen in hemophilia (discussed in Chapter 4), autoimmune disease, older patients and post-partum.

Patients with acquired factor VIII inhibitors present with diffuse bleeding. Unlike classic hemophiliacs, these patients will have large bruises covering large areas of their body. Patient can bleed from any site but the gastrointestinal tract is most common. Post-partum factor VIII inhibitors can appear several weeks after delivery.

Patients will have elevated aPTTs that behave like an inhibitor on the 50:50 mix. Factor levels show a low factor VIII. Sometimes testing is indeterminate between a specific factor VIII inhibitor and lupus inhibitor. Levels of factor VIII will "increase" with dilution of the test plasma in patients with a lupus inhibitor but not with true factor VIII inhibitors. Also, it is rare for patients with lupus inhibitors to have significant bleeding. The strength of the factor VIII inhibitor is reported in "Bethesda Units." Due to the complex kinetics, these levels in acquired factor VIII inhibitors are often difficult to measure and interpret.

Therapy is two-fold, aimed at correcting the hemostatic defect and at driving away the inhibitor. The specific therapy to correct the hemostatic defect is reviewed in detail in Chapter 4.

For very low level inhibitors (<5 BU), treatment is directed toward trying to overpower the inhibitor. With higher level inhibitors prothrombin complex concentrates or activated prothrombin complex concentrate at a dosed 75 units/kg twice/day can be used. Especially in older patients, the use of these products may be complicated by thrombosis.

Porcine factor VIII is useful in the bleeding acquired inhibitor patients. The initial dosing is 100-150 porcine VIII units/kg. Porcine factor VIII should be reserved for the bleeding patient since patients can develop antibodies which cross-react with porcine factor VIII. Anaphylaxis has also been seen.

Now that it is clinically available, recombinant VIIa is becoming the treatment of choice for inhibitor patients. For bleeding patients, the dosing is 90 μg/kg repeated every 2 hours until the bleeding has stopped. For patients who require surgery or have life-threatening bleeding, the rVIIa should be "weaned" by decreasing the dose to every 6 hours for several days after 2-3 days of successful every 2 hour therapy.

Patients with factor VIII inhibitors should receive immunosuppression to eliminate the inhibitor. Up to one-third of patients may transiently respond to immune globulin (1 gram/kg a day for two days). Given the high rate of morbidity, aggressive immunosuppression should be started with prednisone 60mg/day plus oral cyclophosphamide 100mg/day. This should be continued until factor levels increase and the titer decreases. If no response is seen after one month, then other immunosuppressive therapy can be tried. Increasingly it is being reported that patients respond to rituximab therapy (375 mg/m^2/wk x 4) and as more data becomes available this may come into wider use.

Factor IX deficiency rarely occurs as an acquired antibody. Therapy for bleeding is with rVIIa. Immunosuppression is also indicated.

Factor X deficiency Multiple case reports describe factor X deficiency in amyloidosis. The amyloid appears to bind the factor X. Acquired deficiency of factor X appears to be more common in patients with splenic involvement. Patients have responded to therapy with melphalan and prednisone or thalidomide. In patients with massive splenomegaly, splenectomy has been associated with improved factor X levels. In younger patients bone marrow transplant may be an option.

Factor XI deficiency due to inhibitors can be seen in patients with autoimmune disease. These are rarely associated with bleeding.

Factor XIII deficiency is rarely seen with isoniazid or procainamide use. Patients can have severe bleeding with normal coagulation parameters but low factor XIII levels. As with other acquired inhibitors, patients respond to immunosuppression.

Acquired von Willebrand Disease

Acquired von Willebrand disease (vWD) has been reported to occur in lymphomas, myeloproliferative syndromes, myeloma, monoclonal gammopathies and with the use of certain drugs. Acquired deficiency of von Willebrand proteins (vWF) can occur by several mechanisms. One is by protein absorption to the surface of the malignant cell. Malignant cells in lymphomas, myelomas and Wilms tumors can express GP Ib. Another mechanism is by antibody binding to the protein.

The most common drug-induced etiology is administration of hydroxyethyl starch. Bleeding is seen, especially with prolonged use of these agents or with the use of more than 1.5 liters/day. Decreased levels of both vWF and factor VIII are seen, but many patients with have a type 2 defect with selective loss of higher weight vWF multimers. Levels rise after the agent is stopped but some patients may require factor replacement if severe bleeding is present. Rarely, acquired vWD has been reported with valproic acid and ciprofloxacin.

Patients with acquired vWD can present as type 1 (decreased protein) or type 2 (abnormal multimers) disease. The diagnosis is suggested by lack of personal or family history of a bleeding diathesis. Levels of factor VIII, ristocetin cofactor activity and von Willebrand antigen are decreased. Platelet levels of vWF are normal, suggesting depletion of circulating vWF from the plasma. Crossed-immunoelectrophoresis is used to differentiate type 1 from type 2 disease.

Desmopressin is effective in many patients with acquired type 1 and 2. Consistent with the antibody-mediated destruction, the magnitude and duration of desmopressin effect is often reduced in acquired vWD. In some patients it is not effective. Recent reports indicate that high-dose immune globulin is also effective in reversing acquired vWD. For bleeding patients, high doses of Humate-P is indicated with frequent monitoring of factor VIII levels. For patients with very intense inhibitors rVIIa may prove useful. If present, treatment of the hematologic neoplasm is also effective.

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CHAPTER 8

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) may be found in a variety of patients with a variety of disease states. DIC can present with a spectrum of findings ranging from asymptomatic abnormal laboratory findings to florid bleeding or thrombosis. DIC is always a consequence of another process and represents the final common pathway of many processes.

Pathogenesis

DIC is the clinical manifestation of inappropriate thrombin (IIa) activation (Table 8.1). Inappropriate thrombin activation can be due to causes such as sepsis, obstetric disasters and others. The activation of thrombin leads to 1) conversion of fibrinogen to fibrin, 2) activation of platelets (and their consumption), 3) activation of factors V and VIII , 4) activation of protein C (and degradation of factors Va and VIIIa), 5) activation of endothelial cells, and 6) activation of fibrinolysis.

1. **Conversion of fibrinogen to fibrin** leads to formation of fibrin monomers and excessive thrombus formation. In most patients these thrombi are rapidly dissolved by excessive fibrinolysis. In certain clinical situations, especially cancer, excessive thrombosis will occur. In cancer patients this is most often a deep venous thrombosis. Rare patients, especially those with pancreatic cancer, may have severe DIC with multiple arterial and venous thromboses. Non-bacterial thrombotic endocarditis can also be seen in these patients.
2. **Activation of platelets (and their consumption)**. Thrombin is the most potent physiologic activator of platelets so in DIC there is increased activation of platelets. These activated platelets are consumed with resultant thrombocytopenia. Platelet dysfunction is also present. Platelets that have been activated and have released their contents but still circulate are known as "exhausted" platelets which can no longer function to support coagulation. The fibrin degradation products in DIC can also bind to GP IIb/IIIa and inhibit further platelet aggregation.
3. **Activation of factors V, VIII, XI, XIII**. Activation of these factors can promote thrombosis but are then rapidly cleared by antithrombin. This can lead to depletion of all the prothrombotic clotting factors and antithrombin. This can lead to both thrombosis and bleeding.
4. **Activation of protein C** further promotes degradation of factors Va and VIIIa as well as decreasing protein C levels.
5. **Activation of endothelial cells**, especially in the skin, may lead to thrombosis and in certain patients, especially those with meningococcemia, purpura fulminans. Endothelial damage will downregulate thrombomodulin preventing activation of protein C and leading to further reductions in levels of activated protein C.

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Table 8.1. Consequences of excessive thrombin generation

1. Conversion of fibrinogen to fibrin → thrombosis and depletion of fibrinogen
2. Activation of platelets → thrombocytopenia
3. Activation of factors V, VIII, XI, XIII → thrombosis and depletion of coagulation factors
4. Activation of protein C → depletion of factors V and VIII and eventually protein C
5. Activation of endothelial cells → expression of tissue factor
6. Activation of fibrinolysis → lysis of thrombi and depletion of fibrinogen

6. **Activation of fibrinolysis** leads to breakdown of fibrin monomers, formation of fibrin thrombi and increased circulating fibrinogen. In most patients with DIC the fibrinolytic response is brisk. This is why most patients with DIC present with bleeding and prolonged clotting times.

Etiology

In essence, anything that leads to an overproduction of thrombin will cause DIC. This overproduction of thrombin can result from an immense number of clinical situations (Table 8.2). A few of the more common ones are listed below.

Infection can lead to DIC via several pathways. Endotoxin produced by gram-negative bacteria results in expression of tissue factor by both endothelial cells and monocytes. Certain organisms such as Rickettsia and viruses of the herpes family can directly infect endothelial cells, resulting in tissue factor expression. The hypotension produced by sepsis can lead to tissue ischemia and tissue factor expression.

Cancers, primarily adenocarcinomas, can result in DIC. Highly vascular tumor cells are known to express tissue factor. In addition, some tumor cells can express a direct activator of factor X ("cancer procoagulant"). In acute promyelocytic leukemia and to a lesser degree in other leukemias, tissue factor and other enzymes lead to thrombin generation. Patients with DIC in leukemia present with fulminant bleeding syndromes. For mysterious reasons many patients with DIC due to cancer present with thrombosis. This may be due to the inflammatory state which accompanies cancer or it may be a unique part of cancer biology.

DIC due to **obstetrical** causes is rare but can be deadly. Fulminant DIC is a hallmark of amniotic fluid embolism. A fetus retained after dying in utero will lead to DIC within a week due to exposure of maternal plasma to macerated fetal products.

Table 8.2. Etiologies of DIC

Adenocarcinomas
Amniotic fluid embolism
Burns
Intravascular hemolysis
Infections
Leukemia
Penetrating brain injury
Placental abruption
Retained fetal death in utero
Shock
Snake bites
Trauma

Table 8.3. Clinical presentations of DIC

Asymptomatic—laboratory abnormalities only
Severe bleeding—especially from sites of minor trauma such as IV sites
Thrombosis
Purpura fulminans
Severe DIC
Microvascular thrombosis with area of skin ischemia/necrosis

Clinical Presentation (Table 8.3)

Patients can present in one of four ways with DIC.

1. **Asymptomatic**. Patients can present with laboratory evidence of DIC but no clinical problems. This is often seen in sepsis and in cancer. However, with further progression of the underlying disease, these patients may rapidly become symptomatic.
2. **Bleeding**. Most patients with DIC bleed. The bleeding is due to a combination of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis. These patients may present with diffuse bleeding from IV sites, surgical wounds, etc..
3. **Thrombosis**. Despite general activation of the coagulation process, thrombosis is unusual in most patients with DIC. The exceptions include cancer patients, trauma patients, and certain obstetrical patients. Most often the thrombosis is venous, but arterial thrombosis has been reported.
4. **Purpura fulminans**. DIC in association with symmetric limb ecchymosis and necrosis of the skin is seen in two situations. One, primary purpura fulminans, is most often seen after a viral infection. In these patients the purpura fulminans starts with a painful red area on an extremity that rapidly progresses to a black ischemic area. In this situation, acquired deficiency of protein S is often found. These patients will have laboratory evidence of DIC.

   Secondary purpura fulminans is most often associated with meningococcemia but can be seen in any patient with overwhelming infection. Post-splenectomy sepsis syndrome patients are also at risk. Patients present with signs of sepsis; the skin lesions often involve the extremities and may lead to amputations.

Diagnosis

There is no one test that will diagnosis DIC; one must match the test to the clinical situation (Table 8.4).

Screening tests: The PT-INR and aPTT are usually elevated in severe DIC but may be normal or shorted in chronic forms. One may also see a shortened aPTT in severe acute DIC due to large amounts of activated II and factor X "bypassing" the contact pathway. APTT's as short as 10 seconds have been seen in acute DIC. The platelet count is usually reduced but may be normal in chronic DIC. Serum fibrinogen is decreased in acute DIC but again may be in the "normal" range in chronic DIC.

"Specific tests": These are a group of tests which allow one to deduce that abnormally high concentrations of IIa are present.

Ethanol gel and protamine test: Both of these tests detect circulating fibrin monomers. Circulating fibrin monomers are seen when IIa acts on fibrinogen. Usu-

Table 8.4. Testing for DIC

- PT-INR, aPTT, fibrinogen level: non-specific
- Protamine sulfate: detects circulating fibrin monomers. Specific but not sensitive
- Ethanol gel: detects circulating fibrin monomers. Sensitive but not specific
- Fibrin(ogen) degradation products
- D-dimers (fibrin degradation product)

ally the monomer polymerizes with the fibrin clot but when there is too much IIa, these monomers can circulate. Detection of circulating fibrin monomer means there is too much IIa and, ergo, DIC is present.

Fibrin degradation products (FDP): Plasmin acts on the fibrin/fibrinogen molecule to cleave the molecule in specific places. The resulting degradation product levels will be elevated in situations of increased fibrin/fibrinogen destruction (DIC, fibrinolysis). The FDP are typically mildly elevated in renal and liver disease due to reduced clearance.

D-dimers: When fibrin monomers bind to form a thrombus, factor XIII acts to bind their "D" domains together. This bond is resistant to plasmin and thus this degradation fragment is known as the "D-dimer." High levels of D-dimer indicate that 1) IIa has acted on fibrinogen to form a fibrin monomer that bonded to another fibrin monomer and 2) this thrombus was lysed by plasmin.

Other tests that are sometimes helpful:

Thrombin time (TT): This test is performed by adding IIa to plasma. Thrombin times are elevated in: 1) DIC (FDP's interfere with polymerization), 2) the presence of low fibrinogen levels, 3) dysfibrinogenemia, and 4) the presence of heparin (very sensitive).

Reptilase time: This is the same as thrombin time but is performed with a snake venom that is insensitive to heparin. Reptilase time is elevated in the same conditions as the thrombin time with the exception of the presence of heparin. Thrombin time and reptilase time are most useful in evaluation of dysfibrinogenemia.

$F_{1.2}$: $F_{1.2}$ is a small peptide cleaved off when prothrombin is activated to thrombin. Thus high levels of $F_{1.2}$ are found in DIC but can be seen in other thrombotic disorders. This test is still of limited clinical value.

Therapy

The best way to treat DIC is to treat the underlying disease state. However, one must replace factors if depletion occurs and bleeding ensues (Table 8.5). General guidelines for replacement are:

- Protime >INR 2.0 and aPTT abnormal—infuse 10-15 ml/kg of FFP.
- Platelets <50-75,000/μL—give 1 unit of platelet concentrate or one plateletpheresis unit/10 kg body weight.
- Fibrinogen <125 mg/dl—give 10 units of cryoprecipitate.
- Heparin—give only if the patient is having thrombosis.

Plasma replacement is needed to correct multiple factor deficiencies. Past concern about "feeding the fire" is not clinically valid. One should strive to bring the aPTT down to less than 1.5 times normal if possible. Keeping the fibrinogen level over 100 mg/dl is also important.

As mentioned above, platelets are both low and dysfunctional in DIC. Accordingly, a higher goal for platelet levels is needed to compensate.

Table 8.5. Therapy of DIC

- Follow PT-INR, aPTT, platelets and fibrinogen.
- Protime >INR 2.0 and aPTT abnormal—infuse 10-15 ml/kg of FFP.
- Platelets <50-75,000/μL—give 6 platelet concentrates.
- Fibrinogen <125 mg/dl—give 10 units of cryoprecipitate.
- Heparin—give only if the patient is having thrombosis.

Heparin therapy is reserved for the patient with thrombosis. Its use in acute promyelocytic leukemia patients is still controversial. Due to the derangements of coagulation factors, one should follow heparin levels or use low molecular weight heparin instead of following the aPTT. Reliance on the aPTT to follow heparin therapy may lead to over- or under-treatment of patients.

Therapy for purpura fulminans is controversial. Primary purpura fulminans, especially that seen with post-varicella autoimmune protein S deficiency, has responded to plasma infusion titrated to keep the protein S level more than 25%. Anecdotes suggest a response to immune globulin (1 mg/kg x 2 days) or steroids in these patients. Heparin has been reported to control the DIC and extent of necrosis. A reasonable starting dose in these patients is 5-8 units/kg/hr.

Very sick patients with secondary purpura fulminans have been treated with plasma drips, plasmapheresis, and continuous plasma ultrafiltration. Heparin therapy alone has not been shown to improve survival. Much attention has been given to replacement of natural anticoagulants such as protein C and antithrombin III as therapy for purpura fulminans. Multiple randomized trials have shown negative results for the use of antithrombin III. Trials using both zymogen protein C and activated protein C have shown more promise in controlling the coagulopathy of purpura fulminans and improving outcomes in sepsis, especially in patients who also had DIC. For patients with sepsis and DIC or for patients with purpura fulminans, recombinant protein C at the dose of 24 μg/kg/hr should be administered for 96 hours along with aggressive replacement of clotting factors and platelets.

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CHAPTER 9

Liver and Renal Disease

Liver Disease

Patients with liver disease often bleed. This may be due to mechanical reasons such as a ruptured varix or to an underlying coagulopathy. In addition, patients with liver disease require procedures, surgeries and transplantation. Identification and correction of bleeding problems is crucial for good clinical outcomes for these patients.

Pathogenesis of Defects

Patients with severe liver disease have multiple coagulation defects (Table 9.1). These defects are due to:

1. **Decreased coagulation factor synthesis**—Nearly all the major coagulation factors and their inhibitors are synthesized in the liver. The exceptions are factor VIII and Von Willebrand factor. Most factor VIII is synthesized in the liver, but in liver failure the plasma levels are often elevated due to release from endothelial stores.
2. **Thrombocytopenia**—It used to be thought that the hypersplenism which often accompanies liver disease resulted in platelet sequestration. However, it is now appreciated that the liver is the main site of thrombopoietin production and that production is reduced in liver disease, leading to lower platelet production. This explains why splenectomy or shunting procedures often do not improve platelet counts in patients with liver disease. Additionally, patients with hepatitis C appear to have a higher risk of immune thrombocytopenia and may have very low platelet counts.
3. **Platelet dysfunction**—This is due to a number of causes. The reduced clearance of fibrin degradation products and plasmin will lead to platelet dysfunction. Fibrin degradation products can bind and inhibit GP IIb/IIIa. Plasmin will degrade platelet receptors. Also found in patients with liver disease is an ill-characterized increase in the bleeding time. It has been speculated that the increase in nitric oxide levels may result in platelet inhibition. Often the bleeding time is prolonged but the patient has no evidence of increased bleeding. In evaluation of the prolonged bleeding time, one must carefully ask about excessive bleeding with minor trauma. Again, bleeding history is more predictive of future bleeds than is bleeding time.
4. **Increased factor consumption**—Patients with liver disease appear to have an increased consumption of clotting factors. This is due to delayed clearance of activated enzymes leading to increased coagulation. These patients are also more prone to minor and major bleeds leading to increased consumption of factors.

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Table 9.1. Coagulation defects in liver disease

- Decreased synthesis of coagulation factors
- Increased consumption of coagulation factors
- Thrombocytopenia
- Platelet function defects
- Increased fibrinolysis

5. **Primary fibrinolysis**—Liver disease is the most common cause of primary fibrinolysis. This occurs due to a decrease in hepatic production of fibrinolytic inhibitors and delayed clearance of plasmin. There is also data showing that levels of TAFI (thrombin activatable fibrinolysis inhibitor) are low in patients with liver disease. Evidence of enhanced fibrinolysis can be found in 30% of patients with end-stage liver disease. Fibrinolysis is evaluated by measuring the euglobulin clot lysis time. Values of less than 60 minutes (normal being more than 60) indicate a fibrinolytic state. Bleeding seen with fibrinolysis is diffuse bleeding from multiple sites or persistent oozing from surgical sites or minor wounds.

Evaluation and Treatment of Coagulation Defects in Liver Disease

It is important to remember that, despite abnormal laboratory studies, the most common cause of bleeding in liver disease is a mechanical defect (hole in vessel). Thus, evaluation in patients with severe bleeding should be aimed at identifying sites of bleeding. Many patients will have dramatic gastrointestinal bleeding due to bleeding varices or gastric ulcers. In these situations replacement of coagulation factors provides an "adjunctive therapy" role to definitive therapy. Except for certain coagulation defects (thrombocytopenia, fibrinolysis), corrections of mild-to moderate coagulation defects in the severely bleeding patient are probably not important and correction of severe coagulation defects is impossible.

An initial screen of the bleeding patient should consist of the hematocrit, platelet count, PT-INR/aPTT, fibrinogen, D-Dimer and euglobulin clot lysis time (Table 9.2). Since DIC can commonly complicate liver disease, evaluation for DIC should be done on unstable patients with liver disease.

In the rapidly bleeding patient the "magic five" (HCT, PT-INR, aPTT, platelets fibrinogen) should be checked every few hours to guide therapy (Table 9.3). Ideally therapeutic goals should be:

- Protime >INR 2.0 and aPTT abnormal—give 2 units of FFP.
- Platelets <50-75K—give 6 Platelet concentrates or one plateletpheresis unit
- Fibrinogen <125 mg/dl—give 10 units of cryoprecipitate.
- Hematocrit <30%—give packed red cells.

However, it is often difficult to lower the protime in patients with severe liver disease due to the short half-life of factor VII and the minimal changes one achieves with FFP (increase of 5%/unit of FFP for all clotting factors). Consequently, therapy should not be aimed at complete correction of abnormal laboratory values. Overzealous attempts to totally correct the INR are unproductive and will result in volume overload. Also, the increased plasma volume may increase portal pressures, thereby increasing the risk of more bleeding. Keeping the platelet count above 50,000/

Table 9.2. Evaluation of the bleeding patient with liver disease

- PT-INR
- aPTT
- Platelet count
- Fibrinogen level
- Euglobulin clot lysis time
- D-dimer

Table 9.3. Therapy of coagulation defects associated with bleeding in liver disease

- Protime >INR 2.0 and aPTT abnormal—FFP.
- Platelets <50-75k—platelet concentrates.
- Fibrinogen <125 mg/dl—10 units of cryoprecipitate.
- Hematocrit <30%—packed red cells.

μL and the fibrinogen greater than 125 mg/dl is more important than correction of the protime.

Abnormal fibrinolysis is an often overlooked cause of bleeding in patients with liver disease. Bleeding in these patients tends to be characterized by diffuse oozing from minor trauma. Often these patients are futilely treated with massive amounts of fresh frozen plasma before the fibrinolytic defect is discovered. Diagnosis is made by demonstrating a shortened euglobulin clot lysis time. In the patient who is bleeding from fibrinolysis, a trial of antifibrinolytic therapy is warranted. The patient should be screened for DIC and significant urinary tract bleeding. The dose of epsilon-aminocaproic acid (EACA)is a bolus of 4-5 grams given over one hour followed by a continuous infusion of one gram per hour for eight hours. The oral dosing of epsilon-aminocaproic acid is four grams every four hours. The dosing for tranexamic acid is 10 mg/kg IV bolus followed either by 10 mg/kg IV every 6 to 8 hours or 25 mg/kg every 6 to 8 hours orally.

A current area of research is the use of rVIIa for patients with liver disease. Studies have shown shortening of the PT-INR which appears to be effective at achieving hemostasis. Dosing schema are under study, but two doses of 80 μg/kg were effective in preventing bleeding during liver biopsy. There is also data that a single dose of 40 ug/kg administer before intercranial monitor placement can prevent bleeding complications and reduce the risk of fluid overload due to over zealous plasma replacement.

Preparation for Surgery

Patients with liver disease often require surgical procedures. Pre-surgical laboratory screening should consist of the hematocrit, platelet count, PT-INR/aPTT, fibrinogen, D-dimer and euglobulin clot lysis time. Patients with compensated fibrinolysis may rapidly defibrinate during surgical procedures. Before surgery, the platelet count should be increased to over 50,000/μL and the fibrinogen to over 100 mg/dl. Plasma can be used to lower the PT-INR/aPTT but often only a minimal reduction will result. In patients with severe disease it is not feasible to try to lower the INR below 2.0. Recall that an isolated elevation of the INR is indicative of factor VII deficiency and is not associated with increased risk of bleeding. The

patient should be carefully monitored during the procedure and platelets and fibrinogen aggressively replaced.

Liver Transplantation

The advent of liver transplantation has significantly impacted the survival of patients with severe liver disease. Patients may require astonishing amounts of blood during the procedure. Totals of more than 100 units of red cells and plasma are not unusual in these patients. Before liver transplant is considered, baseline coagulations status should be determined. However, baseline coagulation defects are not predictive of bleeding with surgery. Certain operative features are more predictive of bleeding. Patients who have had previous abdominal surgery often require extensive dissection of adhesions and will require aggressive blood support. A long anhepatic time will require frequent checks of the coagulations status and monitoring of replacement products. One should anticipate that when the clamps are released to allow blood flow to the new liver, a "burst" of fibrinolysis will occur. In some patients a heparin-like inhibitor is also released. The coagulopathies that occur during this period are the most challenging. In patients with very severe bleeding one should assay the euglobulin clot lysis time. Severe fibrinolysis should be treated with antifibrinolytic therapy until the patient is stable. If the new liver "takes," the coagulation defects will rapidly resolve.

Uremia

Patients with renal disease can have both a bleeding and a thrombotic diathesis. The thrombotic complications of renal disease are discussed in acquired hypercoagulable states (Chapter 18). Uremic patients may have spontaneous bleeding or may be at risk from bleeding with procedures.

Before the advent of renal replacement therapy, bleeding was a common complication of uremia. Life-threatening bleeding is uncommon, but dialysis patients have a high incidence of gastrointestinal bleeding and subdural hematomas. Patients with end-stage renal disease have a high incidence of underlying gastrointestinal lesions such as angiodysplasia and gastritis which may bleed.

Pathogenesis

The defect in uremia appears to be a platelet function defect. The bleeding time and PFA 100 are usually prolonged. Von Willebrand factor levels are always normal or supranormal. One determinant of the prolonged bleeding time is the hematocrit. Abnormalities of both platelet adhesion and aggregation are seen. The old glass bead retention test that measured platelet adhesion to glass beads is prolonged in uremic patients. Platelet aggregation studies reveal defects in aggregation with ADP and epinephrine. Patients with hematocrits below thirty percent have markedly prolonged bleeding times. It is speculated that with low hematocrits, the red cells flow laminarly and are not able to "push" platelets into the vessel wall. Blood coagulation factors appear not to be affected and unless other problems are present, the PT-INR/aPTT are not prolonged.

Table 9.4. Therapy for uremic bleeding

Acute	
	Aggressive dialysis
	Cryoprecipitate 10 units
	Desmopressin 0.3 μg/kg
Long Term	
	Estrogen 0.6 mg/kg for five days
	Erythropoietin to raise hematocrit over 30%

Evaluation

Uremic patients who are bleeding should have a PT-INR/aPTT and platelet count performed. Patients with uremia are prone to vitamin K deficiency, so assessment of the prothrombin time is important. The half-life of both unfractionated and low molecular weight heparin is prolonged in renal failure. Patients will receive a bolus of heparin with dialysis and the rare patient will have a prolonged anticoagulant effect. Low molecular weight heparins are cleared in the kidneys and if the dose is not adjusted, levels can increase to supranormal levels. Bleeding times are prolonged in renal disease. Unfortunately there is little correlation between prolongation of the bleeding time and actual bleeding, especially with procedures.

Therapy (Table 9.4)

Patients who are severely uremic and are bleeding may respond to aggressive dialysis. If the patient is having life-threatening bleeding, the use of heparin anticoagulants should be avoided.

Infusion of cryoprecipitate has also been shown to correct the bleeding defect. The mechanism of action is unknown. Ten units every twelve hours will correct the bleeding time. Too aggressive use of cryoprecipitate will raise the plasma fibrinogen to very high levels that, theoretically, could promote thrombosis. Also, the effect of cryoprecipitate is not consistent and may fail to halt uremic bleeding.

Desmopressin has been shown to be effective in uremic patients and results in a shorter bleeding time for at least four hours. The reason DDAVP works in uremia is unknown. Since levels of factor VIII and von Willebrand protein are already elevated in uremia, elevation of these proteins appears not to be a mechanism. It has been speculated that DDAVP effect is either via a platelet aggregation promoting effect or via increasing the level of functional von Willebrand protein.

Infusion of conjugated estrogens will shorten the bleeding time. The dose is 0.6 mg/kg/day intravenously for 5 days. The exact mechanism is unknown, but improved vascular integrity has been proposed. One advantage of estrogens is that the effect appears to be long-lasting and can persist for two weeks after infusion.

Raising the hematocrit above 30% will shorten the bleeding time. This can be done either acutely by transfusion or chronically with the use of erythropoietin. It is speculated that increasing the red cell mass will increase platelet-vessel wall interactions. For purposes of hemostasis the target hematocrit with the use of erythropoietin should be greater than 30%.

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CHAPTER 10

Cardiac Bypass

Introduction

More than 500,000 patients undergo cardiopulmonary bypass surgery each year. Coronary bypass surgery may be complicated by blood loss and sometimes a severe bleeding diathesis. Patients presenting for cardiac surgery may have preexisting bleeding defects or may develop severe defects during or after surgery.

Preoperative Coagulation Defects

Anticoagulation. Many patients who present for surgery are already anticoagulated, most often for the underlying heart disease (Table 10.1). If needed, rapid reversal (4-6 hours) of warfarin can be achieved with the use of vitamin K, given as 5 mg over one hour slow intravenous infusion. Alternatively, fresh frozen plasma can be used to prime the cardiac bypass machine. If clinically feasible, patients should stop warfarin one week before the procedure. A therapeutic dose of low molecular weight heparin can be used for anticoagulation. The last dose of heparin should be given the night before surgery.

Congenital heart disease patients have several potential coagulation defects. Patients with cyanotic heart disease and high hematocrits will have spurious elevation of the PT-INR/PTT due to alteration of the plasma/anticoagulant ratio. This occurs with hematocrits of more than 60%. The coagulation laboratory needs to be notified before testing is done. The laboratory can prepare a special tube with the proper amount of anticoagulant for the patient's hematocrit.

Many patients with congenital heart disease have a bleeding diathesis which is associated with a prolonged bleeding time but no obvious platelet abnormalities. The etiology of this defect is unknown, but rare patients may have severe bleeding with surgery or other procedures. If patients are responsive to desmopressin this agent can be given preoperatively.

Table 10.1. Management of patient anticoagulated with warfarin

Elective Procedures
Stop warfarin five days before procedure.
Start enoxaparin 1 mg/kg every 12 hours.
Give last dose evening before surgery and hold morning dose.
Check PT-INR/aPTT morning of surgery.
Emergency Procedures
Stop warfarin.
Give 5 mg slow intravenous push of warfarin if INR greater than 2.0.
If INR still elevated before surgery use 2-4 units of FFP as pump prime.

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Table 10.2. Coagulation defects associated with cardiopulmonary bypass surgery

1. Activation of contact pathway
2. Activation of fibrinolysis
3. Activation of tissue factor pathway
4. Activation of platelets
5. Platelet function defects

Patients with severe pulmonary hypertension can develop acquired type 2A von Willebrand disease. This may be due to destruction of the high molecular weight multimers by the damaged pulmonary endothelium. The affected patients can also have marked thrombocytopenia. These patients can have a severe bleeding diathesis. Patients with pulmonary hypertension and bleeding should undergo a phlebotomy to lower the hematocrit to less than 65%. This reduction in hematocrit can raise the platelet count and ease the severity of the von Willebrand disease.

Cardiopulmonary Bypass

Cardiac bypass results in very complex and still poorly defined defects in all aspects of hemostasis (Table 10.2).

The flowing of blood over artificial surfaces results in activation of the contact coagulation system, leading to factor XIa activation and kinin activation. The activation of the contact pathway is also a potent activator of the fibrinolytic system. The relevance of contact pathway activation has recently been challenged by the persistence of coagulation defects in patients with deficiencies of the contact pathway undergoing bypass.

The tissue factor pathway is also activated during bypass. Monocyte activation is observed with the expression of tissue factor. The inflammatory response to surgery and bypass may also lead to expression of endothelial cell tissue factor. This expression of tissue factor results in persistent thrombin generation during the surgery, despite the large amounts of heparin given during bypass.

Platelets can be activated by contact with the artificial surfaces in the bypass machine. Excessive activation of platelets depletes their granules, leading to the circulation of "spent platelets". Platelet function is also inhibited by loss of the key receptors, GP Ib and IIb/IIIa. This is due in part to cleavage of platelet GP IIb/IIIa by activated proteolytic enzymes and in part to binding of the receptor GP Ib to the artificial surface.

Finally there is activation of the fibrinolytic system. Fibrinolytic activation is via both the contact pathway and by release of endothelial tPA due to the stress of surgery and hypothermia.

Large amounts of heparin are used for the bypass machine to prevent thrombosis of the filters. Levels of heparin can reach as high as five units/ml. These large doses need to be reversed at the end of surgery to prevent bleeding. Since protamine has a shorter half-life than heparin, patients rarely may experience "heparin rebound." High doses of protamine can lead to coagulation defects or the inhibition of platelet function.

The magnitude of the bleeding diathesis is related to surgery length and long "pump runs". Complex dissections, such as those needed during lung transplants or repeat cardiac surgeries, also lead to additional bleeding.

Prevention and Therapy

Prophylactic use of platelets or plasma prior to surgery has been shown to be ineffective except in a few select cases. Patients with pre-existing thrombocytopenia or platelet dysfunction may benefit from pre-operative transfusions to improve platelet function.

The use of desmopressin remains controversial. Initial studies indicated that it could reduce bleeding in cardiac bypass surgery. More recent studies have not confirmed these early trials. In patients with significant blood loss, peri-operative use of desmopressin may help reduce bleeding.

Bypass surgery produces nonspecific activation of many enzymes, especially those of the fibrinolytic system. Therefore, the use of inhibitors of the fibrinolytic system has been advocated. Aprotinin has been the most studied. Aprotinin is a nonspecific inhibitor of many enzymes including those of the fibrinolytic system. It is used during complex cardiopulmonary bypass to decrease blood use. Two regimens have been most studied. The high dose regimen is 2 millions KIU units bolus, two million KIU units in the pump prime and 500,000 KIU/hour of surgery. The low dose regimen is half of these doses. The higher dose regimen has been the most studied. Patients at special risk of bleeding or in whom transfusions are contraindicated (such as Jehovah's Witnesses) benefit the most from use of aprotinin.

Approach to the Bleeding Bypass Patient (Table 10.3)

If the patient is still in the operating suite and starts to have microvascular bleeding, one should check a full panel of coagulation testing including the platelet counts, PT-INR, PTT and fibrinogen. Patients who have had multiple transfusions of cell-saver blood or of packed red cells may have dilutional coagulation defects that need to be replaced with heparin and cryoprecipitate. In the bleeding patient still on bypass, an infusion of desmopressin is indicated. Given a platelet defect, if the PT-INR/aPTT are in the normal range and the patient is still bleeding, transfusion of platelets is indicated, even with platelet counts over 100,000 μL.

If bleeding occurs in the post-operative setting coagulation tests should be run and surgical hemostasis achieved. Again attention should be paid to the PT-INR/PTT and fibrinogen level. Often patients will respond to empiric transfusions of

Table 10.3. Approach to bleeding cardiac surgery patient

Bleeding and Still in Operating Room

1. Check PT-INR, aPTT, fibrinogen and platelet count.
2. Replace any deficits.
3. If still bleeding administer Desmopressin 0.3 μg/kg.
4. If still bleeding administer one platelet transfusion.
5. If still bleeding check euglobulin clot lysis time and if prolonged administer antifibrinolytic agent.

Bleeding Post-Operatively

1. Assess surgical sites.
2. Check PT-INR, aPTT, fibrinogen and platelet count.
3. Replace any deficits.
4. If still bleeding check thrombin time—if elevated give 50 mg protamine.
5. If still bleeding administer one platelet transfusion.
6. If still bleeding check euglobulin clot lysis time and if prolonged administer antifibrinolytic agent.

Table 10.4. Alternative anticoagulation agents for patients with HIT

Argatroban
Bolus 0.1 μg/kg
Infusion of 5-10 μg/kg/min to keep ACT between 300-400 seconds.
Danaparoid
Prime bypass with 3 units/ml
125 unit/kg bolus
7 units/kg/hour infusion during bypass—stop 45 minutes before estimated end of case
Can bolus with 1250 units (750 in patients < 55 kg) if clots seen in circuit.
Lepirudin
Prime bypass with 0.2 mg/ml
0.25 mg/kg bolus
0.5 mg/min infusion 0.5 mg/kg/hr.

platelets. In the immediate postoperative state a thrombin time should be checked to ensure the patient is not having heparin rebound.

Special Situations

Heparin-induced thrombocytopenia (HIT) is common in patients being considered for cardiac surgery. Since anticoagulation is necessary to undergo bypass, the presence of HIT can be a challenge. One strategy is to wait until the titer of the HIT antibody has decreased enough to be undetectable. This clearance of the HIT antibody may take a few weeks. When the platelet aggregation assay or serotonin release assay is negative, the patient can be re-exposed to heparin for a few hours. This window of opportunity can be used for bypass.

The use of the any other anticoagulant can be difficult (Table 10.4). There is limited experience with danaparoid. Unfortunately, danaparoid has a very long half-life and cannot be monitored with the aPTT or ACT. Recommended dosing is 125 units/kg bolus post-thoracotomy followed by 7 units/kg/hour once the bypass is hooked up. The bypass machined should be primed with 3 units/ml. The infusion should be stopped 45 minutes before estimated end of bypass. If patients suffer excessive thrombosis in the bypass machine circuitry, then a bolus of 1250 units (750 if less than 55 kg) can be used.

Hirudin has been used in several cases with monitoring by the ecarin time. 0.20 mg/l should be used in the bypass prime and a bolus of 0.25 mg/kg given to the patient with an infusion of 0.5 mg/kg/hour continued. It is difficult to monitor and can accumulate in patients with renal insufficiency.

Argatroban has been reported to be effective in patients with HIT needing bypass surgery. One recommended dosing strategy is a bolus of 0.1 mg/kg followed by an infusion of 5-10 μg/kg/min to keep the ACT between 300-400 seconds.

"Re-do's": Patients who present for a repeat cardiac surgery are at high risk for significant bleeding. These patients require complex dissections of tissue planes and will have greater blood loss. They will have longer "pump runs" and a higher incidence of bypass -induced coagulation defects. All of these patients should receive aprotinin.

Left ventricular assist devices (LVAD) are being frequently used either as a "bridge" to transplantation or to support a patient during an episode of severe heart failure. Early devices required aggressive anticoagulation and resulted in high rates

of both bleeding and thrombosis. Newer devices use textured surface to provide a rugged surface and thus do not require anticoagulation.

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CHAPTER 11

Immune Thrombocytopenia

Introduction

Immune thrombocytopenia (ITP) is a common condition affecting about 1:20,000 individuals. Unfortunately, much controversy exists about all aspects of the disease with little "hard" data to base decisions on.

Pathogenesis and Epidemiology

ITP is due to antibodies binding to platelet proteins, most often to the platelet receptor GP IIb/IIIa. These antibody-coated platelets then bind to Fc receptors in macrophages and are ingested. The initiating event in ITP is unknown. It is speculated that the host responds to a viral or bacterial infection by creating antibodies which cross-react with the platelet receptors. Continued exposure to platelets perpetuates the immune response. ITP that occurs in childhood appears to be an acute response to a viral infections and usually resolves. ITP in adults may occur in any age group but is seen especially in young women. Adult ITP can resolve in 30% of patients but may require splenectomy or chronic therapy.

Symptoms

Patients first present with petechiae—small bruises 1 mm in size on the shins. True petechiae are only seen in severe thrombocytopenia. Patients will also notice frequent bruising and bleeding from the gums. Patients with very low platelet counts will notice "wet purpura"—blood-filled bullae in the oral cavity. Life-threatening bleeding is a very unusual presenting sign unless other problems (trauma, ulcers) are present. The physical examination is only remarkable for stigmata of bleeding such as the petechiae. The presence of splenomegaly weighs strongly against a diagnosis of ITP.

Diagnosis

Extremely low platelet counts with a normal blood smear and a negative history is diagnostic of ITP. One should question the patient carefully about drug exposure (see drug-induced thrombocytopenia), especially about over-the-counter medicines, "natural" remedies or recreational drugs.

There is no laboratory test that "rules-in" ITP; rather, it is a diagnosis of exclusion. The blood smear should be carefully examined for evidence of microangiopathic hemolytic anemias (schistocytes), bone marrow disease (blasts, teardrop cells) or any other evidence of a primary bone marrow disease. In ITP, the platelets are larger than normal. One should exclude pseudo-thrombocytopenia, which is the clumping of platelets due to a reaction to the EDTA anticoagulant in the tube. The diagnosis is established by drawing the blood in a citrated (blue-top) tube to perform the platelet count.

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

There is no role for anti-platelet antibody assays given that this test lacks sensitivity and specificity. In a patient without a history of autoimmune disease or symptoms, empiric testing for autoimmune disease is not recommended.

The role of bone marrow examination is controversial. Patients with a classic presentation (young woman, normal blood smear) do not require a bone marrow exam before therapy is initiated. Some authorities recommend bone marrow aspiration before splenectomy or before cytotoxic therapy is started. Patients who do not respond to initial therapy should also have a bone marrow aspiration. The rare entity of amegakaryocytic thrombocytopenia can present with a similar clinical picture to ITP but amegakarocytic thrombocytopenia will not respond to steroids. Bone marrow aspiration reveals the absence of megakaryocytes. It is rare, however, that another hematological disease is diagnosed in patients with a classic presentation of ITP.

In the future, measurement of thrombopoietin and reticulated platelets may provide clues to diagnosis. Patients with ITP paradoxically have normal or only middy elevated thrombopoietin levels. The finding of a significantly elevated thrombopoietin level should lead to questioning of the diagnosis. One can now measure "reticulated platelets" which are analogous to the red cell reticulocytes. Patients with ITP (or any platelet destructive disorders) will have high levels of reticulated platelets. These test are not recommended for routine testing but may be helpful in difficult cases.

Therapy

Therapy in ITP should be guided by the patient's signs of bleeding and not by slavish adherence to numbers. In general, patients tolerate thrombocytopenia well. It is unusual to have life-threatening bleeding with platelet counts over 1,000/μL in the absence of mechanical lesions. Rare patients will have antibodies that interfere with the function of the platelet, and these patients can have profound bleeding with only modestly lowered platelets counts.

The primary therapy of ITP is prednisone at a dose of 60-80 mg/day started at the time of diagnosis.(Table 11.1) Most patients will respond by one week although some patients may take up to 4 weeks to respond. When the platelet count is above 50,000 μL the prednisone should be tapered over the course of several weeks. An alternative to prednisone is dexamethasone 40 mg/day for 4 days. This may induce a rapid rise in the platelet count but it is unknown if there is any long-term advantage over prednisone. One advantage of dexamethasone is that patients only need to take medication for four days.

Two treatments can be tried for rapid induction of a response. Intravenous immune globulin (IVIG) at 1 gram/kg repeated in 24 hours or intravenous anti-D antibody at 75 μg/kg single dose can induce a response in over 80% of patients in 24-48 hours. Immunoglobulin has several drawbacks. One is that it may cause aseptic meningitis. Anther is that in patients with vascular disease, the increased viscosity can induce ischemia. The use of anti-D is limited to Rh positive patients who have not had a splenectomy but because of ease of use (one dose over 15 minutes) it is the first option in eligible patients. It should not be used in patients who are Coombs positive for fear of provoking more hemolysis.

For patients who are severely thrombocytopenic and do not respond to initial therapy there a two options for raising the platelet counts. One is to use combination therapy of IVIG plus anti-D plus methyprednisolone plus vincristine. The combination of IVIG and anti-D may be synergistic since they block different Fc receptors.

Table 11.1. Acute therapy of ITP

Prednisone 1 mg/kg—taper when count is over is 50,000/μL over the course of four weeks
For bleeding patients or counts below 5-10,000/μL
- Immune globulin 1 gram/kg iv repeat in 24 hours or
- Anti-D (WinRho) 75 μg/kg once

Refractory patients
- Immune globulin 1 gram/KG IV plus
- Anti-D 75 μg/kg plus
- Methyprednisolone 30 mg/kg plus
- Vincristine 1.3 mg/m^2 (capped at 2mg) *or*
- Immune globulin 1 gram/kg continuous infusion over 24 hours and
- Continuous infusion platelets (one plateletpheresis unit/ 6 hours or one platelet concentrate/hour)

The other options is to infuse a continuous "drip" of platelets (one unit over 6 hours) and IVIG for 24 hours.

Patients with severe thrombocytopenia who relapse with reduction of prednisone or who do not respond to prednisone have several options. In some patients, repeated doses of anti-D or IVIG can transiently raise the platelet count, and some patients may only need several courses of therapy. Another option is to try a six-month course of pulse dexamethasone 40 mg/day for 4 days, repeated every 28 days.

In patients with severe thrombocytopenia who do not respond or who relapse with lower doses of prednisone, splenectomy should be strongly considered. Splenectomy will induce a good response in 60-70% of patients and is durable in most patients. Splenectomy carries a short-term surgical risk and the life-long risk of increased susceptibility to overwhelming sepsis. However, the absolute magnitude of these risks is low and is often lower than that of continued prednisone therapy or of continued cytotoxic therapy.

Unfortunately, there are still about 30% of patients with ITP who fail splenectomy. These patients who fail splenectomy are very difficult to manage, and the lack of reliable data makes choosing other therapy difficult. (Table 11.2) Multiple treatment options exist:

Rituximab 375 mg/m2 weekly for four weeks has recently been shown to be very active in ITP. Patients either show a rapid response or may take up to eight weeks for their counts to go up. Although experience is limited, the response seem to be durable, especially in those patients whose counts rise over 150,000/μL and in patients who relapse, a response can be re-induced with a second course.

Danazol 200 mg/qid is thought to downregulate the macrophage Fc receptor. The onset of action may be delayed and a therapeutic trial of up to 4-6 months is advised. Danazol is very effective in antiphospholipid antibody syndrome patients with ITP and may be more effective in pre-menopausal women. Once a response is seen danazol should be continued for 6 months and then an attempt should be made to see if the agent can be weaned.

Vincristine 1.4 mg/m^2 weekly has a low response rate but if a response it going to be seen it will occur rapidly within two weeks. Thus, a prolonged trial of vincristine is not needed; if no platelet rise is seen in several weeks the drug should be stopped.

Table 11.2. Therapeutic options in splenectomy failures

- Rituximab 375 mg/m^2/wk x 4 weeks
- Azathioprine 125 mg/day
- Cyclophosphamide 1 gram/m^2 repeated every 28 days
- Danazol 200 mg/qid +/- azathioprine
- Dexamethasone 40 mg/day x 4 days repeated every 28 days for six months

Azathioprine 150 mg po daily, like danazol, demonstrates a delayed response and requires several months to assess for response. Recently it has been reported that the related agent mycophenalate 1000 mg bid is also effective in ITP.

Cyclophosphamide 1 gm/m^2 IV repeated every 28 days has been reported to have a high response rate. Although considered more "aggressive", this is a standard immunosuppressive dose and should be considered in patients with very low counts. Patients who have not responded to single agent cyclophosphamide may respond to multi-agent chemotherapy.

A Practical Approach to the Refractory Patient

One approach is to divide patients into "bleeders" and "nonbleeders". Bleeders have either very low platelet counts (under 5,000/μL) or have had significant bleeding in the past. Non-bleeders have platelet counts above 5,000/μL and no history of severe bleeding.

Bleeders who fail splenectomy should receive aggressive therapy with immunosuppression. One approach to is first start with rituximab since it is not cytotoxic. If rituximab does not work then one can consider bolus cyclophosphamide. If this is unsuccessful, then one can consider using combination of azathioprine plus danazol. Since it may take 4-6 months for this combination to work, these patients may need frequent IVIG therapies to maintain a safe platelet count.

Nonbleeders should be tried on danazol and other relatively "safe" agents. If this fails rituxan may be considered. Before one considers cytotoxic therapy, the risk of the therapy must be weighed against the risk of the thrombocytopenia. The mortality from ITP is fairly low (5%) and is restricted to patients with severe disease. Patients with only moderate thrombocytopenia and no bleeding are better served with conservative management. There is little justification for the use of continuous steroid therapy in this group of patients given the long-term risks of therapy.

Clinical trials are now underway to explore more effective therapy for refractory ITP. Patients, especially those with refractory disease, should be strongly urged to enroll in these trials.

Surgery

Patients with ITP who need surgery either for splenectomy or for other reasons should have their platelet counts raised to a level above 20 - 30,000/μL before surgery. Most patients with ITP have augmented platelet function and will not have excessive bleeding with these platelet counts. For patients with platelet counts below this level, an infusion of immune globulin or anti-D may rapidly increase the platelet counts. If platelet transfusion is required, the platelets should be leukoreduced to

avoid stimulating anti-HLA antibodies and predisposing the patient to platelet alloimmunization.

Pregnancy

Up to 2% of pregnant women will develop low platelet counts during their pregnancy. The most common reason is "gestational thrombocytopenia". This is an exaggeration of the lowered platelet count seen in pregnancy women. Counts may fall as low as 50,000/μL at the time of delivery. No therapy is required as the fetus is not affected and the mother does not have an increased risk of bleeding.

Pregnancy complications such as HELLP syndrome and thrombotic microangiopathies also present with low platelet counts but these can be diagnosed by history.

Women with ITP can either develop the disease during pregnancy or have a worsening of the symptoms. Counts often dramatically drop during the first trimester. Early management should be conservative with low doses of prednisone to keep the count above 30,000/μL. Immunoglobulin is also effective but there are rare reports of pulmonary edema. Rarely patients who are refractory will require splenectomy which may be safely performed in the second trimester.

Most controversy centers around management of the delivery. In the past it was feared that fetal thrombocytopenia could lead to intracranial hemorrhage, and Caesarean section was always recommended. It now appears that most cases of intracranial hemorrhage were due to alloimmune thrombocytopenia and not ITP. Furthermore the nadir of the baby's platelet count is not at birth but several days after.

Attempts have been made to measure the fetal platelet count either before birth with percutaneous umbilical cord sampling or by measuring scalp platelet counts. Both of these approaches have been fraught with error. It appears the safest course is to proceed with a vaginal delivery and then immediately check the baby's platelet count. If the platelet count is low in the neonate, immunoglobulin will raise the count. Since the neonatal thrombocytopenia is due to passive transfer of maternal antibody, the platelet destruction will abate in 4-6 weeks.

Evans Syndrome

Evans syndrome is defined at the combination of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). These diseases can present simultaneously or sequentially. Patients with Evans syndrome are thought to have a more severe disease process, more prone to bleeding, and to be more difficult to treat.

The classic clinical presentation of Evans syndrome is severe anemia and thrombocytopenia with the cytopenias tending to be resistent to initial steroid therapy.

Children with Evans syndrome often have complex immunodeficiencies. In adults, Evans syndrome most often complicates other autoimmune diseases such as lupus. There are increasing reports of Evans sydrome occurring as a complication of T-cell lymphomas. Often the autoimmune disease can predate the lymphoma diagnosis by months or even years.

Several disease processes can present with both hemolysis and thrombocytopenia (Table 11.3). Patients with congenital hemolytic syndromes are often thrombocytopenic, perhaps due to splenomegaly. Laboratory evidence of severe hemolysis and thrombocytopenia are the presenting signs of thrombotic microangiopathies.

Table 11.3. Differential diagnosis of Evans syndrome

- Congenital hemolytic syndromes
- Hemolytic uremic syndrome
- Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia
- Thrombotic thrombocytopenic purpura
- Wilsons disease

Many patients with paroxysmal nocturnal hemoglobinuria will be thrombocytopenia. In patients with liver disease both Wilsons disease and spur cell anemia are rare causes of severe hemolysis.

In theory the diagnostic approach is straightforward by showing a Coombs positive hemolytic anemia in the setting of a clinical diagnosis of immune thrombocytopenia. The blood smear will show spherocytes and a diminished platelet count. The presence of other abnormal red cell forms should raise the issue of an alternative diagnosis.

It is uncertain how vigorous one should search for other underlying diseases. Many patients will already have the diagnosis of an underlying autoimmune disease. The presence of lymphadenopathy should raise the concern for lymphoma. The diagnosis of T-cell lymphomas can be difficult to make with the biopsied nodes often appearing "reactive." Often DNA studies for T-cell receptor clonality are required for diagnosis.

Initial therapy is high dose steroids (2 mg/kg/day). Intravenous immunoglobulin should be added if severe thrombocytopenia is present. Patients who cannot be weaned off prednisone or relapse after prednisone should be considered for splenectomy although these patients are at higher risk of not responding. For patients who fail splenectomy aggressive immunosuppression should be considered. A reasonable choice would be bolus cyclophosphamide 1 gram/m^2. There are also increasing reports of the use of rituximab but the response rate remains uncertain. For patients with Evans syndrome due to underlying lymphoma, antineoplastic therapy often results in prompt resolution of the symptoms. Recurrence of the autoimmune cytopenias often herald relapse.

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CHAPTER 12

Thrombotic Microangiopathy (TTP/HUS)

Introduction

The thrombotic microangiopathies (TM) are a group of diseases which share the traits of microvascular occlusion, thrombocytopenia, and microangiopathic hemolytic anemia. Common to these diseases are a dramatic presentation and often fulminant illness. Although these diseases share some common characteristics, course and prognosis may vary.

Classification

Since the underlying pathophysiology and etiology of many of the TMs are unknown, any classification scheme is imprecise (Table 12.1). In addition, many of the signs and symptoms of TM overlap, especially thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). However, several classic syndromes do stand out. TTP and HUS are the opposite ends of a spectrum of disease involving TM, renal disease, and multi-organ system involvement. Pregnancy is associated with a unique TM, known as HELLP syndrome, which consists of hemolytic anemia, elevated liver function tests and low platelets. The characteristic presentations of TTP and HUS may also occur during pregnancy and the post-partum period. Finally, some drugs are associated with HUS-like syndromes. This chapter will discuss TTP in detail and compare and contrast it with the other syndromes.

Table 12.1. Classifaction of thrombotic microangiopathies

TTP
Classic TTP
Relapsing TTP
Chronic TTP
HUS
Typical HUS
Atypical HUS
Pregnancy-Related HUS
Pregnancy-related TTP
HELLP syndrome
Post-partum HUS
Therapy-Related HUS
CSA/FK 506 HUS
Bone marrow transplant HUS
Drug-related HUS

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Table 12.2. Thrombotic thrombocytopenic purpura: Pentad

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal insufficiency
- Fever
- Mental status changes

Classic Thrombotic Thrombocytopenic Purpura (TTP)

Clinical Presentation

Many patients with TTP will first have a prodrome of a flu-like or diarrheal illness. Patients can present with a variety of conditions ranging from general malaise to sudden death. The disease can strike at any age, although the predominant age is 20-40 years of age. Women are affected more than men in a 2:1 ratio.

The classic reported pentad of fever, mental status changes, renal insufficiency, thrombocytopenia and microangiopathic hemolytic anemia is seen in less than 40% of patients (Table 12.2). As described below, the pentad can range in severity from mild to severe.

Neurological

Neurological complaints range from mild confusion to a stroke-like syndrome. Most patients with TTP will have neurological complaints, although in mild cases these symptoms must be elicited by direct questioning. Patients complain of tiredness, confusion, and headaches. Seizures are common and may be recurrent. Patient can also develop transient focal neurological defects which may wax and wane over several hours.

Hematologic

The diagnostic criteria for TTP and other TMs depend on the hematologic picture. By definition of the syndrome, patients are thrombocytopenic. This is because of spontaneous aggregation of platelets and their deposition on damaged endothelial surfaces. The platelet count may range from 80,000/μL in mild cases of TTP to less than 1,000/μL in severe cases. The median platelet count is 20,000/μL. In mild cases of TTP, the thrombocytopenia is mistakenly ascribed to other etiologies and diagnosis is delayed. The platelet function is impaired due to continual platelet activation; this leads to the concept of "spent platelets". Even though a seemingly adequate number of platelets are circulating, they are unable to support hemostasis. Thus, clinical bleeding is often present with platelet counts which are not dramatically decreased.

The hematocrit in TTP is low due to hemolysis. Patients will have high reticulocyte counts and elevated LDH and indirect bilirubin. A Coombs test will be negative. Review of the peripheral smear is diagnostic for the microangiopathic hemolytic anemia. One should carefully examine the smear for red cell fragments. Often in very ill patients rare schistocytes will be present, but in TTP and other TM there is at least one red cell fragment per high-powered field. The presence of microangiopathic hemolytic anemia is the *sine qua non* for diagnosis of any TM. The LDH is strikingly elevated, often over two to four times normal. The source of the LDH is not only lysed red cells. On fractionation, LDH fraction 5 and 4 are increased, suggesting damage beyond just the red cells.

The patient's coagulation status can be otherwise normal. The markers of DIC such as FDP's and D-dimers may be absent or present in only low titers (i.e., 1-2 μg/dl).

Renal

Patients with TTP present with renal insufficiency and, unlike HUS, rarely renal failure. The creatinine is usually only mildly to moderately elevated. Often the urinalysis will show hemoglobinuria and mild proteinuria.

Gastrointestinal

Patients can present with ileus and frank bowel necrosis from ischemia. Pancreatitis due to small bowel infarction may also be seen.

Pulmonary

Although not classically described, patients may present with pulmonary infiltrates and respiratory insufficiency

Cardiac

Patients will often have signs of cardiac ischemia such as arrhythmias due to myocardial microinfarctions. Many patients who die of TTP will have sudden death suggesting that cardiac ischemia/infarction may play a prominant role in fatal cases.

Pathogenesis

The etiology of TTP is unknown, but it is somehow related to massive in-vivo platelet activation resulting in platelet microthrombi and vascular damage. Our understanding of the role of von Willebrand factor is emerging. When von Willebrand factor is first synthesized, it is a very large polymer that is reduced by a protease known as ADAMTS13 (**A D**isintegrin **A**nd **M**etalloprotease domain with **T**hrombo**S**pondin type I motifs) to less than 20 million in molecular weight. The very large polymers can cause spontaneous platelet aggregation without first binding to collagen. Very large von Willebrand multimers are found in patients with TTP. Data has accumulated showing that many patients with the classic form of TTP have antibodies directed against ADAMTS13. This would fit with the observations that TTP occurs more often in young women, in patients suffering from lupus, can be recurrent, and may respond to immunosuppressant therapy. However, it appears that many patients with classic TTP have normal levels of ADAMTS13, so other factors must be involved in stimulating platelet aggregation.

Differential Diagnosis

Given the variety of non-specific symptoms associated with TTP, accurate diagnosis may be difficult. As mentioned, the classic pentad is present in only 40% of patients. Patients seen initially are often given a variety of diagnoses ranging from alcohol withdrawal to septic shock syndrome. Since TTP may be seen in patients with lupus, confusion exists between the two diagnoses. One report indicates that 24% of patients dying with lupus cerebritis had pathologic evidence of TTP. TTP should always be thought of, especially in young patients who develop a dramatic multisystem illness unexpectedly. TTP is a treatable disorder. It is essential to review the smear in any sick patient with even mild thrombocytopenia to assess for the presence of schistocytes. Despite recent elucidation of reduced activity of ADAMTS13, this is not a consistent finding and it is unclear whether this will ever be a clinical useful assay.

Table 12.3. TTP: Therapy

- Prednisone 60-120 mg/day.
- 1-1.5 plasma volume plasma exchange, using plasma as replacement fluid.

Therapy (Table 12.3)

Untreated TTP is rapidly fatal. Mortality in the pre-plasma era ranged from 95 to 100%. Present day plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to less than 20%. However, despite adequate therapy, patients often die either of refractory disease or suddenly during the early course of therapy.

Steroids in doses of 60 mg/day intravenously of prednisone are routinely given. This should be continued until the patient has fully recovered. Very mild cases of TTP (no neurologic symptoms) may be treated with prednisone alone with institution of plasma exchange at the slightest hint of disease progression.

Plasma infusion is beneficial, perhaps due to replenishing deficient ADMATS13. Plasma exchange has been shown to be superior to simple plasma infusion. This may be due to the ability of plasma exchange to deliver very large volumes of fresh frozen plasma. In patients who cannot be immediately exchanged, plasma infusions should be started at a dose of one unit every 4 hours.

Plasma exchange demonstrated a superior outcome compared to use of plasma transfusions. Patients with all but the mildest cases of TTP should receive 1-1.5 volume plasma exchanges for at least five days. Plasma exchange should be continued daily until the LDH has normalized. Patients should then be weaned off, starting with every-other day exchange. If the platelet count falls or LDH rises, every-day exchange should be reinstated. Since the platelet count can be affected by a variety of external influences, the LDH tends to be a more reliable marker of disease activity.

Platelet transfusions are contraindicated in patients with TTP. Transfusions of platelets sometimes leads to clinical deterioration of the patient. After platelet transfusion patients can develop respiratory failure or seizures. Platelet transfusion should be limited to truly life-threatening situations such as intracranial hemorrhage. In most patients with TTP there is very little justification for platelet transfusion. In severely thrombocytopenic patients, line placement for plasma exchange should be performed by an experienced person. This approach to line placement has been shown to be safe in patients with coagulation defects.

Refractory Patients (Table 12.4)

Patients with TTP vary in their response to plasma exchange. Patients with refractory disease can present with two general patterns: the patient who slowly responds or who responds rapidly but continues to require daily plasma exchange or the patient who worsens while on exchange.

Slow responders often just require patience. Some patients will require several weeks of exchange before they recover. In patients with active but stable disease anecdotal evidence exists regarding the effectiveness of infusion of vincristine (1mg/m^2 IV, capped at 2 mg on day 1 and then 1 mg on days 4,7, and 10) or immunoglobulin 1 g/m^2 for two days. Patients should be for evaluated for other causes of thrombocytopenia such as heparin-induced thrombocytopenia, folate deficiency ,or thrombocytopenia due to other drugs such as antibiotics.

Table 12.4. Options to consider for refractory patients

- Cryo-poor plasma
- Twice daily 1 plasma volume plasma exchange
- Vincristine 1.4 mg/m^2 day 1 and then 1 mg days 4, 7, and 10
- Rituximab 375 mg/m^2 weekly x 4 therapy for refractory TTP

Patients who worsen while being treated are fortunately rare but present difficult challenges. In a patient with TTP who is worsening one should ensure the patient does not have another syndrome such as vasculitis or an *Ehrlichia* infection. These processes may present with a microangiopathy and multisystem failure. One maneuver which may be helpful in the worsening patient is to increase the exchange volume to 1.5 plasma volumes or to exchange one volume twice per day. Use of vincristine or gammaglobulin may be indicated. Like for many other hematologic disease, reports are increasing that rituximab may be usefull for these patients. Although splenectomy has been advocated, it is risky in the seriously ill patient with TTP. Splenectomy should only be considered as a desperate measure.

Other Thrombotic Microangiopathies

Relapsing TTP

Between 30-60% of patients successfully treated for TTP may relapse. Relapse can either be early (less than 30 days after stopping plasma exchange) or late. Early relapses are often due to inadequate therapy and can be severe. Late relapses can range in severity. Some patients will present early on with subtle signs while others will present with seizures. Relapsing patients typically respond to standard TTP therapy. In patients with early relapse, one should continue therapy until there is clearly no evidence of disease activity.

Chronic TTP

Rare patients have frequent attacks of TTP which may occur almost on a monthly basis. The etiology of this is unknown but is likely autoimmune or, in young patients, genetic. These patients often require monthly plasma infusion to control their disease. Some patients have responded to immunosuppression with cyclophosphamide, azathioprine, or rituximab.

Hemolytic Uremic Syndrome (HUS)

HUS was recognized as a separate syndrome in 1954. Classically, it is the triad of renal failure, microangiopathic anemia and thrombocytopenia. Two major forms are recognized, a “typical” form seen in young children with a prodrome of diarrhea and an “atypical” form.

Typical HUS

Typical HUS (also referred to as HUS D+) is seen in children under the age of four. Children often have a prodrome of diarrhea, usually bloody. Children come to medical attention due to symptoms of renal failure. In HUS, thrombocytopenia can be mild in the 50,000/μL range. Extra-renal involvement is common in typical HUS. Neurologic involvement can be seen in 40% of patients with seizure being the predominant feature. Elevated liver function tests are seen in 40% of patients,

and 10% of patients will have pancreatitis. Patients with classic HUS will respond to conservative therapy and renal replacement therapy. Severe cases or those with prominent extra-renal manifestations respond to plasmapheresis. Unfortunately, although most patients recover some renal function, many patient will have long-term renal damage.

Atypical HUS

Atypical HUS is defined as "a HUS syndrome which lacks the typical features". This description obviously lacks diagnostic precision. In general this term has been applied to HUS which has prominent extra-renal symptomatology. HUS in older patients and HUS without preceding diarrhea fit this category. The prognosis is thought to be worse for atypical HUS. Therapy for atypical HUS is plasma exchange. Patients with atypical HUS, especially older patients, may require months of plasma exchange several times each week to control their disease. Often they will have chronic renal disease or failure.

Pregnancy-Related TM

Pregnancy-Related TTP

TTP can occur anytime during pregnancy, often leading to diagnostic confusion due to the overlapping clinical presentation between TTP and HELLP syndrome. There does appear to be a unique presentation of TTP which occurs in the second trimester at 20-22 weeks. The fetus is uninvolved with no evidence of infarction or thrombocytopenia if the mother survives. The pregnancy appears to promote the TTP since the TTP will resolve with termination of the pregnancy and can recur with the next pregnancy. Therapy includes termination of the pregnancy or attempting to support the patient with plasma exchange until delivery. Up to 30% of patients will relapse with future pregnancies so this information must be weighed in planning future pregnancies.

HELLP Syndrome

Weinsten introduced the acronym HELLP syndrome to describe a variant of pre-eclampsia. The acronym HELLP syndrome (Hemolysis, Elevated Liver tests, Low Platelets) describes a variant of pre-eclampsia. Classically, HELLP syndrome occurs after 28 weeks of gestation in a patent suffering from pre-eclampsia. The pre-eclampsia need not be severe. The first sign is a drop in the platelet count followed by abnormal liver function tests. Signs of hemolysis are present with abundant schistocytes on the smear and a high LDH. HELLP can progress to liver failure and deaths are also reported due to hepatic rupture. Unlike TTP, fetal involvement is present in the HELLP syndrome with fetal thrombocytopenia reported in 30% of cases. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will most often result in cessation of the HELLP syndrome, but refractory cases will require dexamethasone and plasma exchange. Patients should be closely observed for 1-2 days after delivery as the hematologic picture can transiently worsen before improving. A severe variant of HELLP syndrome is seen in patients with antiphospholipid antibody disease who may present at 20-24 weeks with HELLP. These patients may have continuing thrombosis refractory to heparin and may require pregnancy termination to stop the process.

Post-Partum HUS

An unusual complication of pregnancy is an HUS syndrome seen up to 28 days post-partum. This form of HUS is severe, and permanent renal failure often results.

Therapy-Related HUS

TM are seen commonly in patients receiving a number of therapies. These TMs can range from being an indication for adjustment of therapy to a rapidly fatal disorder.

Cyclosporine (CSA)/FK 506 HUS

The first case of TM associated with CSA was reported soon after its introduction. Commonly it is seen after the CSA is started with the appearance of a dropping platelet count, falling hematocrit, and rising LDH. Some cases have been fatal. However, the TM often resolves with decreasing the dosage of the offending medicine or changing to another agent. The newer agent FK 506 is also implicated in TMs. The etiology appears to be direct endothelial or renal damage caused by these drugs. Thrombocytopenia and microangiopathy may only reflect vascular damage.

Bone Marrow Transplant TM

TTP/HUS can complicate both autologous and allogeneic bone marrow transplants. The incidence ranges widely depending on the criteria used to diagnosis TTP/HUS but it is in the range of 15% for allogeneic and 5% for autologous bone marrow transplants. Several types of TTP/HUS are recognized in bone marrow transplantation. One is "multi-organ fulminant" which occurs early (20-60 days), has multi-organ system involvement and is often fatal. This has also been associated with severe CMV infections. Another type of TTP/HUS is similar to cyclosporin/FK 506 HUS. A third type is the "conditioning" TTP/HUS which occurs six months or more after total body irradiation, and is associated with primary renal involvement. Finally, patients with systemic CMV infections will present with a TTP/HUS syndrome related to vascular infection with CMV. The etiology of bone marrow transplant-related TTP seems different from that of "classic" TTP. Alterations of the von Willebrand factor cleaving protease have not been found in BMT-related TTP. This would seem to implicate therapy-related vascular damage. The therapy of bone marrow transplant TTP/HUS is uncertain. Patients should have their cyclosporine or FK506 doses reduced. Although plasma exchange is often tried, patients with fulminant or conditioning TTP/HUS often fail to respond.

Drug-Related TM

TTP/HUS is most commonly seen with the antineoplastic agent mitomycin C, with an incidence of 10% when a dose of more than 60 mg is used. The onset is slow, with the first sign being a falling platelet count months after therapy has been stopped. This is followed by a relentless course of renal failure and death. A characteristic feature of mitomycin C TTP/HUS is the occurrence of a non-cardiac pulmonary edema with red cell transfusions. Anecdotal reports state that treatment with staphylococcal A columns may be useful for this condition. Since advanced cancer itself can be associated with a TTP-like syndrome, the thrombocytopenia and hemolysis may be due to the cancer and not the cancer treatment.

Although TTP/HUS have been reported with other anti-neoplastic drugs including carboplatinum and gemcitabine, the newest drug now featured in case reports is ticlopidine, which has an incidence of TTP of 1:1600. Since this drug is often prescribed for patient with vascular disease, these patients may be initially misdiagnosed as having recurrent strokes or angina. Patients seem to respond to plasma exchange but mortality rates of up to 50% have been reported. TTP/HUS has also been reported with clopidogrel but with a considerably lower incidence.

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CHAPTER 13

Non-Blood Product Agents for Bleeding Disorders

Several non-plasma-derived agents exist for therapy of bleeding disorders (Table 13.1). All of these agents share the common qualities of being relatively non-specific and having potential life-threatening complications.

Desmopressin

Desmopressin (DDAVP) is a synthetic analog of anti-diuretic hormone. Administration of desmopressin in normal volunteers raises the levels of both factor VIII and von Willebrand proteins several-fold. In patients with mild factor VIII deficiency, desmopressin can raise levels 2-3 times. The factor VIII levels achieved may support hemostasis for minor surgeries and dental procedures. In von Willebrand disease the response depends on the type of disease. Most type 1 patients and some type 2A will have a robust response to desmopressin. Type 2B and pseudo-von Willebrand patients may develop severe thrombocytopenia with desmopressin. Patients with factor XI deficiency have also been reported to occasionally respond to desmopressin.

The reason administration of desmopressin leads to this increase in factor VIII is unknown. Direct administration of desmopressin to endothelial cells does not result

Table 13.1. Non-blood product agents for bleeding disorders

Desmopressin	
IV: 0.3 μg/kg over 30 minutes	
Nasal:	Over 50 kg - one squirt of 150 μg in each nostril
	Under 50 kg - one squirt of 150 μg total
Aminocaproic Acid	
IV: 5 gram bolus, then 500 - 1000 mg/hour	
Oral: 5 gram bolus, then 2 grams every two hours	
Tranexamic Acid	
IV: 10 mg/kg every 6-8 hours	
Oral: 25 mg/kg every 6-8 hours	
Aprotinin	
High-dose regimen: 2 millions KIU bolus, 2 million KIU in the pump prime and 500,000 KIU/hour of surgery.	
The low dose regimen is: 1 million KIU bolus, 1 million KIU pump prime and 250,000 KIU/hour of surgery	
Conjugated Estrogens	
0.6 mg/kg IV for five days	

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in von Willebrand protein release, implying the presence of a second messenger or some other indirect effect.

Desmopressin is also useful in patients with some congenital bleeding disorders. Patients with inherited platelet disorders may respond to desmopressin. Finally, approximately half of patients with bleeding and prolonged bleeding times but no identifiable defect will respond to desmopressin.

Patients with uremia will also demonstrate shortening of the bleeding time with desmopressin. This may be due to a rise in newly released von Willebrand factor.

Patients with inherited bleeding disorders should be tested for their response to desmopressin. Patients with factor VIII deficiency should have factor VIII levels done before and 45 minutes after the infusion ends. Patients with von Willebrand disease should have a von Willebrand panel and bleeding time or PFA-100 performed before and after. Patients with platelet dysfunction should just have bleeding times PFA-100 performed.

Desmopressin is available in two forms. The intravenous form is dosed as 0.3 μg/kg mixed in normal saline and infused over 15 -30 minutes. It takes 45 minutes after dosing to achieve full hemostatic effect. A nasal form of desmopressin (Stimate) is also available. Each squirt contains 150 μg of desmopressin. The dose for patients over 50 kilograms is one squirt in each nostril, and for those under 50 kilograms one squirt total. Patients who use Stimate should be instructed in its use to ensure proper application of the medicine. It is also essential that patients are actually prescribed Stimate and are not given generic desmopressin. The generic desmopressin is dosed for enuresis, not vWD, and contains an inadequate dose.

Since desmopressin is an analog of antidiuretic hormone, water retention is the major side effect. For most patients with occasional use of the drug this is not a problem. However, in surgical patients who are receiving intravenous free water and desmopressin, life-threatening hyponatremia may result. Surgical patients and other patients who cannot control their fluid intake should have serum sodium and urine output monitored.

Rare reports of patients with pre-existing vascular disease receiving desmopressin and then developing thrombosis exist. It is unclear what risk desmopressin poses to patients with underlying vascular disease.

13

Aminocaproic Acid and Tranexamic Acid

Aminocaproic acid and tranexamic acid function as antifibrinolytic agents by blocking the binding of plasmin to fibrinogen. These agents are useful in three situations. One is in the presence of excessive fibrinolysis. This most often occurs with liver disease but it may rarely complicate amyloidosis or rare congenital defects. Antifibrinolytic agents are also useful as adjunctive therapy for oral or dental procedures in patients with a bleeding diathesis. Finally, in patients with severe thrombocytopenia, the use of antifibrinolytic agents may reduce bleeding.

The major hazard associated with these drugs is the fact that they strengthen thrombi and prevent lysis of thrombi. In areas of confined bleeding such as ureteral hemorrhage, use of antifibrinolytic agents may lead to obstruction. In the presence of DIC where fibrinolysis is a secondary process, the use of antifibrinolytic agents may induce severe thrombosis. Long-term use of aminocaproic acid has been associated with the development of a generalized myopathy.

The dose of aminocaproic acid is a bolus of 5 grams given over one hour followed by a continuous infusion of one gram per hour. Oral regimens vary. One

approach is to use a 5 gram oral bolus and then give 2 grams every two hours immediately after an oral procedure for the first day, cutting back to 4 grams every 4 hours for the next 2 days.

The dosing for tranexamic acid is 10mg/kg IV bolus followed either by 10 mg/kg IV every 6 to 8 hours or 25 mg/kg every 6 to 8 hours orally. The oral dosing of tranexamic acid makes it useful for oral surgery.

Aprotinin

Aprotinin is a non-specific protease inhibitor which inhibits fibrinolytic enzymes as well as a variety of other enzymes. Aprotinin has been shown in cardiac surgery to reduce the use of blood products. This may be due to preservation of platelet function as well as inhibition of fibrinolysis. The dosing and indications for aprotinin are evolving. Patients undergoing cardiac bypass who are at higher risk for bleeding—repeat cardiac operations, prior use of aspirin, underlying bleeding diathesis—benefit the most from aprotinin. Two regimens have been studied most. The high dose regimen is 2 million KIU units bolus, 2 million KIU units in the pump prime and 500,000 KIU/hour of surgery. The low dose regimen is half of these doses.

The major adverse reaction to aprotinin is anaphylaxis. While rare with initial use, the incidence may reach five percent with repeated use of the agent. All patients should receive a test dose of aprotinin before drug administration.

Aprotinin also prolongs the activated clotting time (ACT). If the ACT is being used to monitor heparin levels, the effect of aprotinin must be taken into account or else the patient will be underdosed with heparin. Different ACT reagents react differently with aprotinin and the product literature should be consulted.

Conjugated Estrogens

High doses of conjugated estrogens have been reported to ameliorate bleeding in patients with uremia. The dosing is 0.6 mg/kg per day intravenous or orally for five days. The hemostatic effect of estrogens can last for 2 weeks. The reason estrogens are effective in slowing uremic bleeding is unknown.

Recombinant VIIa (rVIIa)

Although initially developed for use in hemophilia patients with inhibitors, there are more and more reports of the use of rVIIa for complex bleeding diatheses (Table 13.2). Clinical settings include trauma patients, patients with liver disease, patients bleeding while being anticoagulated with novel anticoagulants such as hirudin, and warfarin overdoses. Much of this data exists in case series and isolated reports. Exact

Table 13.2. Current uses of rVIIa (NovoSeven)

- Factor VIII inhibitors
- Factor IX inhibitors
- Factor XI deficiency
- Factor VII deficiency
- Glanzmann thrombasthenia
- Severe liver disease
- Reversal of warfarin
- Reversal of hirudin
- Reversal of fondaparinux

dosing recommendations are still being studied but a reasonable approach would be to use the 90 μg/kg dose for bleeding trauma patients and 40 μg/kg for patients with liver disease and warfarin overdose.

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CHAPTER 14

Transfusion Therapy and Massive Transfusions

Many patients with bleeding disorders will require transfusion of blood products. This chapter will summarize the use of blood products for hemostasis. This chapter will also discuss the art of managing a massive transfusion.

Platelets

Description (Table 14.1)

One platelet concentrate (one unit of random donor platelets) is derived from one unit of donor blood. Single-donor plateletpheresis can be used to harvest platelets. One unit of single donor (pheresis) platelets is equivalent to 6-8 platelet concentrates. Single-donor platelets offer the advantage of exposure to only one blood donor. One platelet concentrate can raise the platelet count by 5-7,000/μL. Platelets are mildly "stunned" while in storage and it takes four hours for transfused platelets to be fully functional in the circulation. A pool of five platelet concentrates contains enough plasma to be the equivalent of a unit of FFP (all coagulation factors except the labile V and VIII). HLA-matched platelets are single-donor pheresis units that are from an HLA-matched donor. This product should only be ordered if there is evidence of HLA antibodies in the recipient. If the response to platelet transfusion is poor, always check platelet counts 15 minute after platelet infusion. A poor 15 minute platelet count may be indicative of HLA antibodies. A good 15 minute platelet count but poor 24 hour count is more suggestive of consumption—fever, sepsis, drugs, etc.. This scenario is not an indication for HLA-matched platelets.

Table 14.1. Platelet products

Platelet Concentrates
One donor
Dose: 1 unit per 10 kilogram of body weight
Plateletpheresis Platelet Product
One donor
Dose: one per adult patient
HLA-Matched Platelets
One donor matched for 1-4 class I HLA antigens
Dose: one per adult patient

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Indications

There is no scientific basis for the old "20,000/μL" cut-off for the transfusion of platelets. Risk of spontaneous severe bleeding rises only when the platelet count is below 5,000/μL. Risk of intracranial hemorrhage is highest only when the count is below 1,000/μL (risk 0.76%/day). The Gmur study demonstrated a rate of major bleeding of 0.07%/day when platelets counts were 10-20,000/μL. This risk of major bleeding rose to 1.9%/study day when platelet counts were less than 10,000/μL. Patients with chronic autoimmune thrombocytopenia can tolerate platelet counts in the 5-10,000/μL range for years. Considerable data from randomized trials now indicates that, for oncology patients, a transfusion trigger of 10,000/μL is sufficient to prevent thrombocytopenic bleeding. There are trials suggesting that one can even eliminate "prophylactic" platelet transfusions. However, these trials only eliminated transfusions for very stable patients—no fevers, petechia, etc... and the applicability of this approach to usual clinical practice is uncertain.

One should order "single-donor plateletpheresis product" when giving patients platelets. Although not always available, use of this product will expose the patient to one donor instead of six to eight. In patients who are expected to have multiple transfusions (those with leukemia, etc.) consider giving leukodepleted platelets to reduce the risk of alloimmunization. The dose of single donor units is 1 unit per 10 kg of ideal body weight. Typically this is 6 - 8 units in an adult patient.

In patients who are actively bleeding or who have DIC one should consider a platelet transfusion trigger higher than 10,000/μL. A platelet count of 50,-75,000/μL is recommended as there is some data that, at least for massive transfusions, this will stop microvascular bleeding.

Platelet transfusions are not indicated for stable thrombocytopenic patients with platelet counts over 10,000/μL. Also, transfusion of platelets may worsen TTP or heparin-induced thrombocytopenia.

Platelet Alloimmunization

Patients exposed to cells with different HLA types will develop antibodies to HLA antigens. This is most common in patients who have received previous transfusions of blood that was not leukodepleted, or in patients who have been pregnant. Since platelets carry class I HLA antigens they will be rapidly destroyed by HLA antibodies. As many as 90% of patients transfused for aplastic anemia or myelodysplasia will become HLA-immunized. The incidence of HLA-immunization is lower in patients receiving chemotherapy. In the older literature this incidence was reported to be as high as 60 - 90% but appears to be lower nowadays. Patients who have developed HLA antibodies usually respond better to platelets matched for HLA antigens. Unfortunately, some patients will either have a rare HLA type or are so heavily immunized that they will not respond to any platelet transfusion.

The importance of alloimmunization centers on two concepts—recognition and avoidance. Patients with HLA antibodies will often fail to have an immediate increment in platelet count with transfusions. One can test for anti-HLA antibodies if there is no bump in platelet count 15 minutes after transfusion. However, some patients have antibodies with specificity against specific platelet proteins and not HLA antigens. Patients with these type of antibodies will not respond to HLA-matched platelets. Patients who plan to undergo bone marrow transplant or aggressive chemotherapy, who have been pregnant, or who have been previously transfused should be evaluated for anti-HLA antibodies. This permits planning of

Table 14.2. Evaluation and management of platelet alloimmunization

1. Check platelet count 15 minutes after platelet transfusion.
2. If rise in platelet count is less than 5,000/μL, check for HLA antibodies.
3. Administer HLA-matched platelets and evaluate for response.
4. If three HLA-matched platelet transfusions are ineffective, stop giving.
5. In completely refractory patients:
   A. evaluate for other causes of thrombocytopenia (HIT, drugs).
   B. give one unit of platelets/day.
   C. consider antifibrinolytic therapy
      1. Epsilon aminocaproic acid 1 gram/hour iv, or
      2. Tranexamic acid 10 mg/kg every eight hours.

transfusion needs. The evidence suggests that transfused white cells are responsible for initiating the anti-HLA response. Trials have shown that giving leukodepleted blood products may reduce the incidence of alloimmunization. Patients who are not HLA-alloimmunized should receive only leukodepleted products.

Management of the Platelet-Refractory Patient

Patients who are refractory to platelet transfusion present a difficult clinical problem (Table 14.2). If patients are demonstrated to have HLA antibodies, one can transfuse HLA-matched platelets. Unfortunately, platelet transfusions do not work in 20 - 70% of these patients. HLA-matched platelets are matched for anywhere from 1 - 4 HLA loci. Some loci are difficult to match so good matches may be unavailable. As many as 25% of patients have anti-platelet antibodies in which HLA-matched products will be ineffective. One can perform platelet cross-matching to find compatible units for these patients but this may not always be successful. In the patient who is totally refractory to platelet transfusion, consider drugs as an etiology of antiplatelet antibodies (especially vancomycin). Use of antifibrinolytic agents such as epsilon aminocaproic acid or tranexamic acid may decrease the incidence of bleeding.

Fresh Frozen Plasma (FFP)

Description

Fresh frozen plasma is derived from one unit of donated whole blood. The average volume of FFP is 225 ml. One unit of FFP can raise coagulation factor levels by 8% and fibrinogen by 13 mg/dl in the average patient. FFP takes about 30 minutes to thaw.

Indications

FFP should only be used when there is a documented coagulation defect that can be corrected by a reasonable amount of FFP. It is useful for the overdosed warfarin patient who is bleeding or needs immediate surgery. Otherwise, if reversal is necessary, vitamin K should be used. DIC with bleeding is another indication for FFP. FFP is used along with plasma exchange in thrombotic thrombocytopenic purpura. FFP may be useful in the bleeding patient with liver disease and documented coagulation defects although most bleeding in this group of patients is due to "mechanical" reasons (i.e., hole in a varix). Since FFP contains the anticoagulant proteins C and S and antithrombin III, it is used to provide these anticoagulant factors for deficient patients undergoing surgery.

FFP is not indicated for most of the purposes for which it is commonly used. FFP seems often to be thought of as a "Super Glue" for any type of bleeding or any type of abnormality in coagulation testing (e.g., slightly prolonged PT). Use of FFP for any but the indications listed above is both a waste of product and a needless exposure of the patient to viral diseases. One example of inappropriate use is the stable patient with end-stage liver disease who has a coagulopathy. Assuming his factor VII is 25% of normal, it would take more than six units of FFP (1.2 liters) to increase it to 75%. Since the half-life of factor VII is seven hours, keeping his factor VII above 50% would require six units of FFP every six hours. This is almost five liters of FFP per day. To keep the factor VII level above 100% would require 18 units of FFP every six hours (15 liters/day).

Although there is a paucity of data to support this, most specialists believe that a PT lower than an INR of 2.0 is safe for surgeries and procedures, assuming no other coagulation defects exist.

Cryoprecipitate

Description

Cryoprecipitate is derived from one unit of fresh frozen plasma that is thawed at 4 degrees Celsius. The precipitate is resuspended with 10 ml of saline or FFP, and re-frozen for storage. One unit contains at least 150 mg of fibrinogen and 80 units of factor VIII, along with von Willebrand factor and factor XIII (Table 14.3). Cryoprecipitate takes about 20 minutes to thaw.

Indications

Cryoprecipitate is useful to quickly increase the fibrinogen level in patients with DIC or in patients with massive transfusion and resulting hemodilution. It is third-line therapy in the treatment of Type 1 von Willebrand disease and is second-line therapy in patients with other types of von Willebrand disease. Currently Humate-P is the preferred replacement product for von Willebrand disease. Cryoprecipitate can be used as a source of factor VIII for hemophiliacs, but the preferred product for these patients is the super-pure factor VIII concentrates. Cryoprecipitate can also be used to shorten the bleeding time of uremic patients, but the results are variable for this indication.

Corrections of Defects before Procedures in Patients with Liver Disease and Other Coagulopathies

Questions often arise with regard to the need to give FFP or platelets to a patient before procedures to correct coagulation abnormalities. This has been studied in several patient groups. In patients with liver disease, those undergoing paracentesis or thoracentesis with INRs of up to 3.8 and platelet counts as low as 50,000/uL had no increased incidence of bleeding. A retrospective study of liver transplant patients with coagulopathies revealed no bleeding complications despite attempts at correcting coagulopathy. Data from our institution suggests a low incidence of bleeding with line placement in patients with coagulation defects if lines are placed by experienced operators who have placed more than 50 lines.

If a procedure is emergent, the person with the most experience should perform the procedure. If time permits, coagulation defects that are simple to correct such as thrombocytopenia should be corrected. However, coagulation factors will not compensate for poor procedural skills.

Table 14.3. Components in cryoprecipitate

- Factor VIII
- Factor XIII
- Fibrinogen
- Von Willebrand factor

Massive Transfusions

Massive transfusion is defined as giving more than one blood volume in 24 hours or less. It is more practically defined as giving one blood volume in two hours or less. Patients requiring massive transfusion will require close attention to detail and careful monitoring for complications.

The complications that can be seen with massive transfusions are hyperkalemia, hypothermia and hypocalcemia. Hypothermia is the most common. Red cells are stored at 4 degrees Celsius and the infusion of red cells rapidly cools the patient. Rapid transfusers that also warm the blood should be used for these patients. Keeping the patient warm with thermal blankets is also useful. Core temperatures below 35 degrees has been associated with development of coagulopathies and a variety of metabolic disturbances.

Hyperkalemia is rarely seen. Massive amounts of citrate may lead to transient hypocalcemia. However, citrate is rapidly metabolized and clinical hypocalcemia is rarely a problem. One should not replace calcium empirically as this has been associated with worse outcomes. If calcium is of concern, measuring the ionized calcium can guide therapy.

Coagulation defects are common in massive transfusions. These may be due to dilution of the plasma by massive fluid resuscitation or by red cell transfusions. Packed red cells contain little plasma, and massive replacement of blood volume with only packed red blood cells can lead to a dilutional coagulopathy. Patients may also develop a coagulopathy due to underlying medical conditions or due to trauma.

One cannot predict the degree of coagulopathy from the number of blood transfusions. Some patients may receive 20 units of packed red cells and still have good hemostatic function. Others may have florid coagulopathies due to injuries before the first unit of blood is given. Therefore, it is crucial to monitor the patient's coagulation status during massive transfusions.

Managing Massive Transfusions

The approach to massive transfusions is to measure five laboratory tests which will reflect the basic parameters essential for both blood volume and hemostasis (Table 14.4). The tests are:

1. Hematocrit
2. Platelet count
3. Prothrombin time (INR)
4. Activated partial thromboplastin time
5. Fibrinogen level

Replacement therapy is based on the results of these laboratories with these guidelines (Table 14.5):

For a platelets count less than 50-75,000/μL, a plateletpheresis concentrate or 6-8 pack of single-donor platelet concentrate is given to the patient. Since the platelets are suspended in plasma, this transfusion will also provide plasma to the patient.

Table 14.4. Five basic tests for management of massive transfusions

1. Hematocrit
2. Platelet count
3. Prothrombin time (INR)
4. Activated partial thromboplastin time
5. Fibrinogen level

Table 14.5. Management of massive transfusions

1. Rapidly obtain basic five tests.
2. Assess need for empiric platelet or cryoprecipitate transfusion.
3. Assess need for products based on results of basic five tests:
   A. Platelets <50-75,000/μL—give platelet concentrates or 6-8 pack of single donor platelets.
   B. Fibrinogen <125 mg/dl—give 10 units of cryoprecipitate.
   C. Hematocrit below 30%—give red cells.
   D. Protime >INR 2.0 and aPTT abnormal—give 2-4 units of FFP.

For a fibrinogen level less than 125 mg/dl, 10 units of cryoprecipitate should be given. This should raise fibrinogen by 100 mg/dl.

For INR 2.0 with an abnormal aPTT, give 2-4 units of FFP. Isolated elevation of the INR does not require replacement therapy.

For an aPTT greater than 1.5 times normal, give 2-4 units of plasma.

For a hematocrit below 30%—if the patient is bleeding or hemodynamically unstable—give red cells.

Priority should be directed toward keeping the platelet count about 50-75,000/μL. Low platelet counts are the largest determinant of microvascular bleeding in massively transfused patients. The fibrinogen should be kept above 100 mg/dl. Low fibrinogen, along with preventing hemostasis, also results in prolongation of the INR and aPTT. Patients with marked abnormalities of the PT and INR (aPTT > 2 times normal) should receive aggressive therapy with at least four units of plasma. Minor abnormalities of PT-INR and aPTT should be judiciously treated with plasma.

One should repeat the basic five laboratory tests after administering the blood products. This allows one to ensure that adequate replacement therapy was given for the abnormal laboratories. Frequent (every 4-6 hours) checks of the coagulation laboratories also allows rapid identification and therapy of new coagulation defects before they become severe. A flow chart of the laboratories and the blood products administered should also be kept.

Occasionally, empiric therapy of the severely bleeding patient is required. One should start with platelet products. In patients likely to also have severe DIC (i.e., head trauma patients) empiric administration of 10 units of cryoprecipitate is indicated.

Two common abnormalities found after massive transfusions are isolated elevations of the PT and a massively prolonged aPTT. Factor VII is very labile, and often patients will have a mildly prolonged PT with normal INR for hours to days after massive transfusions. As mentioned before, this minor prolongation of the INR is irrelevant to bleeding risk and should not be treated. If both the PT and aPTT are

very prolonged (>100 seconds), then the fibrinogen should be checked. Fibrinogen levels below 80 mg/dl interfere with the endpoints of the PT/aPTT determinations and will lead to spuriously high results. A very prolonged aPTT with only a minor elevation of the PT is suggestive of heparin contamination. This can be a common occurrence in the hectic management of massive transfusions.

Suggested Reading

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CHAPTER 15

Deep Venous Thrombosis and Pulmonary Embolism

Natural History

At least 250-300,000 patients per year in the United States suffer a first deep venous thrombosis, with 5 to 10 per 10,000 population suffering a thrombotic event each year.

It is estimated that pulmonary emboli hospitalize at least 250,000 people in the United States per year and that at least 32,000 of those die from thrombosis. More than 90% of pulmonary emboli occur as a complication of thrombosis in the deep venous system of the legs. Therefore, treatment and prevention of deep venous thrombosis will reduce the occurrence of pulmonary embolism. Another key point is that more than 90% of the deaths from pulmonary embolism occur in the first hour. Thus, management is aimed toward prevention of a repeat embolism and not treatment of the initial embolus. It is estimated that the mortality rate of untreated pulmonary embolism is 30-40%, and the risk of pulmonary embolism from untreated proximal deep venous thrombosis is 50-80%.

Diagnostic Tests for Pulmonary Embolism and Deep Venous Thrombosis

Clinical Signs and Symptoms—Patients first notice dyspnea and cough following a pulmonary embolism. Chest pain occurs hours to days after the event with development of lung infarction. One-third of patients will have hemoptysis, and 10-20% will have syncope. Most patients on exam will have tachypnea (70-92%) but less then half have tachycardia (30% of patients in the classic PIOPED study). Chest x-rays are normal in only 30%. A nonspecific infiltrate is seen in 50-70%, and an effusion in 35%. In the PIOPED study 15% of patients had PO_2 greater than 90 mmHG and 20% had alveolar-arterial gradients less than 20 mmHG. These results demonstrate that patients with pulmonary embolism need not be hypoxic or have an abnormal a-A gradient.

Prediction Rules—Recently there has been great interest in clinical prediction rules for deep venous thrombosis and pulmonary embolism. Using these rules, clinicians can better predict which patients are at higher risk of thrombosis. Several examples exists (Tables 15.1 and 15.2). The best validated for DVT are the Well's criteria, and two prediction rules have also been validated for PE. Use of these prediction rules helps in interpreting non-diagnostic studies and may be used as described below along with the D-dimer to determine whether patients should be evaluated for thrombosis.

D-dimer—A major advance in evaluation of patients with DVT/PE is the wide availability of rapid D-dimers assays. Thrombi have areas which are growing and

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Table 15.1. Clinical probability score for deep venous thrombosis

Variable	Points
Active Cancer	+1
Paralysis or recent plaster immobilization of lower extremity	+1
Recently bedridden for > 3 days or major surgery within 4 weeks	+1
Local tenderness	+1
Calf Swelling greater than 3mc than asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema in symptomatic leg	+1
Dilated superficial veins (non-varicose) in symptomatic leg only	+1
Alternative diagnoses as or more likely than DVT	-2

Score ≥ 2 DVT likely, < 2 DVT unlikely
Wells PS. NEJM 2003; 349:1227.

Table 15.2. Clinical probability score for pulmonary embolism

Variable	Points
Clinical signs and symptoms of DVT	+3
PE as likely or more likely than alternative diagnosis	+3
Immobilization or surgery in past four weeks	1.5
Previous PE or DVT	1.5
Heart rate more than 100/min	1.5
Hemoptysis	1
Active cancer	1

Low probability <2, moderate probability 2-6 and high probability > 6
Wells Ann Int Med 135: 108, 2001.

Variable	Points
Previous DVT or PE	+2
Heart rate > 100	+1
Recent surgery	+3
Age:	
60-79	+1
>80	+2
$PaCO_2$	
< 36 mmHg	+2
36-40 mmHg	+1
$P0_2$	
<50 mmHg	+4
50-59 mmHg	+3
60-69 mmHg	+2
70-79 mmHg	+1
Atelectasis	+1
Elevated hemi-diaphragm	+1

Low Probability 0-4, Intermediate probability 5-8, High >9
Wicki Arch Int Med 161:92, 2001

other areas which are undergoing fibrinolysis. It has been shown that all patients with clinically significant thrombosis will have levels of D-dimers above 500 μg/ml. Confusion arises because there are three different types of D-dimer assays available, all with different abilities to help in diagnosing DVT/PE.

The D-dimer study used for diagnosis of DIC is the latex agglutination test. It is designed for high levels of D-dimers seen with DIC and is NOT sensitive enough for DVT diagnosis. This type of D-dimer assay should never be used in the diagnostic evaluation of DVT/PE.

"Rapid" point of care D-dimer assays such as the SimpleRed are slide assays devised to read positive if the D-dimer is above 500 ng/ml. These types of assays are less sensitive (80-90%) than the rapid ELISA but are simple to use and require no special equipment to run. The rapid D-dimer is most effective when used with a clinical prediction rule. Thus, a patient with a negative D-dimer and low probability of thromboembolic event has a very low chance of having thrombosis and need not be evaluated further. If a patient has either a more than low probability of DVT/PE or positive D-dimer then they need to be further evaluated for thrombosis.

The "rapid ELISA" or "high-sensitivity" assay for D-dimer offers near 100% sensitivity for DVT. Accordingly a patient with a negative ELISA D-dimer requires no further evaluation. The rapid ELISA assay requires special equipment to perform the test.

The other drawback of the D-dimer test is its lack of specificity. Therefore, patients with positive D-dimer assays require further testing to establish the presence of thrombosis. Patients with recent trauma or recent surgery, pregnancy, or who are over age 70 have a higher baseline D-dimer level which greatly limits the use of D-dimers in these patients.

CT scan—The newer high resolution CT scanners such as helical CT have demonstrated the ability to image pulmonary emboli in the larger pulmonary vessels. In many institutions CT scans are rapidly replacing other methods for diagnosing pulmonary embolism. CT scans have high specificity for pulmonary embolism but are only highly sensitive to central and segmental pulmonary arterial embolism. The overall sensitivity of CT for pulmonary embolism appears to be as low as 70%. Therefore, a negative CT scan *does not* rule out the diagnosis of pulmonary embolism. Also, the specificity of CT for PE is lower for clots in the sub-segmental distribution. These caveats must be balanced by the fact that CT scans are often readily available and may also lead to diagnosis of non-thrombotic causes of pulmonary symptoms.

V/Q scans are sensitive but not specific for pulmonary embolism. Interpretation is best viewed as "*high probability*," "*negative*" and "*non-diagnostic*." High probability scans are specific if the patient has not had a previous pulmonary embolism (90%) but this falls to 73% in patients with previous pulmonary emboli. The specificity is 83% in patients with cardiac or pulmonary disease. Only 40-50% of patients with pulmonary emboli will have high probability scans. An abnormal chest x-ray is found in 70% of patients with pulmonary embolism. Unless the chest x-ray defect is small or not in a non-perfused area, this will make the scan intermediate or low probability. Low probability scans do not rule out pulmonary embolism! As many as 20-36% of patients with pulmonary embolism will have low probability scans. In PIOPED, a high clinical suspicion coupled with a low probability scan yielded a 40% rate of pulmonary embolism. Generally, 15-25% of patients with low probability scans will have pulmonary emboli. In a recent prospective study, 7.8% of sick patients with low probability scans died of autopsy-proven pulmonary embolism. An absolutely normal scan does confidently rule out pulmonary embolism. Unless a patient

has a high probability scan or a normal scan one will need to do further studies to establish the diagnosis of pulmonary embolism. Furthermore a high probability scan is only diagnostic for pulmonary embolism in patients with a high pretest probability for pulmonary emboli.

Leg studies are the definitive diagnostic test in patients with symptoms of deep venous thrombosis. Furthermore, leg studies aid in the patient with a non-diagnostic V/Q scan or negative CT scan. Deep venous thrombosis will be present in 50-70% of patients with proven pulmonary embolism. If deep venous thrombosis is present, this establishes the need for anticoagulant therapy and eliminates the need for angiography. In one study the use of leg studies reduced the need for angiography from 43% to 26% after indeterminate V/Q scans.

Venogram used to be the gold standard. Venograms visualize both the calf and deep veins. Drawbacks of venography include dye load and a 5% risk of actually causing thrombosis. Given that very few venograms are currently performed, the accuracy and ability to perform technically adequate studies is greatly reduced.

Duplex ultrasound has a 93% sensitivity and 98% specificity for diagnosing proximal deep venous thrombosis in symptomatic patients. Duplex has a lower sensitivity (70-80%) for detection of calf deep venous thrombosis. In cases of a negative study and suspicion of pulmonary embolism, one needs to either perform follow-up duplex to rule out clot extension or do angiography if the suspicion of deep venous thrombosis or pulmonary embolism is high.

Pulmonary angiography is the gold standard for diagnosis of pulmonary embolism. Angiography is invasive with a mortality rate of 0.5% and morbidity of 2-4%. These risks are lower than that of empiric anticoagulation or of ignoring a pulmonary embolism.

Diagnostic Approach

Deep venous thrombosis. If available, a negative rapid high sensitivity D-Dimer eliminates the need for further evaluation of patients suspected of having DVT. If the high-sensitivity assay is not available, then clinical probability of DVT should be assessed. If the clinical probability is not low, then doppler-ultrasound of the lower extremities is performed. If this is positive, the patient requires antithrombotic therapy. If it is negative and the patient had a low pre-test probability for DVT then no further scans are done. Otherwise the scan should be repeated in one week.

Pulmonary embolism (Figs. 15.1 and 15.2). Unfortunately there are still many approaches to the diagnosis of PE. If a high sensitivity D-dimer is available and it is negative or the patient has a low probable of PE AND a rapid D-dimer is negative then no further studies are needed.

If further evaluation is required, then one approach is to obtain a CT scan. If this is positive for embolism, treatment can be started. Since a negative CT scan does not rule out embolism, further testing is needed. In this case leg studies are useful. If positive for DVT then the need for therapy is established. If negative then the test can either be repeated in one week or, if the patient is very ill, angiography can be done. The patient with a negative CT scan and low clinical probability of PE need not be studied further.

If a V/Q scan is obtained and if the scan is normal, an embolus is ruled out. If the scan is read as high probability in a previously healthy patient with a high prestest probability, this is diagnostic. For indeterminate scans, the legs should be studied. A positive leg scan mandates therapy and no further testing is required. If the leg scan is negative, then the approach is tailored to the patient's state of health. For patients

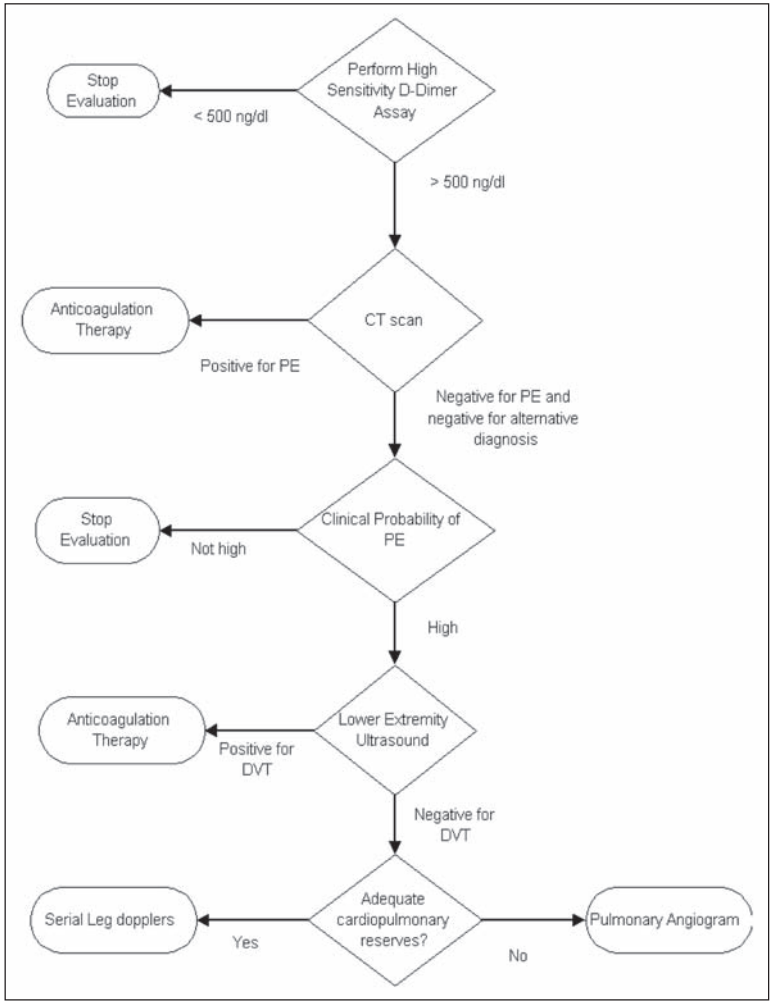

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Fig. 15.1. Diagnostic flowchart for pulmonary embolism using high sensitivity D-dimer.

with good cardiopulmonary reserve who are also reliable, angiography can be avoided by repeating the leg scan one day and one week later. Studies have shown patients with indeterminate V/Q scans and persistently negative leg scans have a low risk of recurrent thrombosis. Patients who are ill should undergo pulmonary angiography.

Immediate Therapy

Heparin—See following section.

Thrombolytic therapy—Given the natural history of pulmonary embolism, the role of thrombolytic therapy is uncertain. That thrombolytic therapy lyses clots

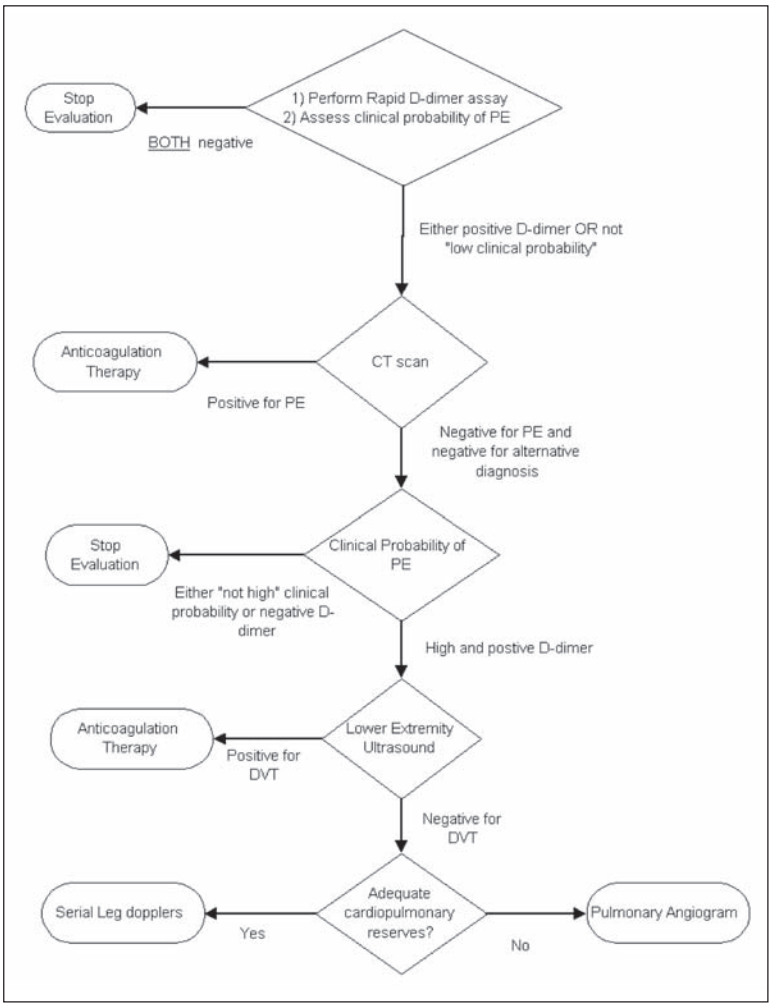

Fig. 15.2. Diagnostic flowchart for pulmonary embolism using point of care D-dimer.

faster then heparin was of no clinical significance in the large trials of the early 1980s or in more recent trials. For example, 24-hour lung perfusion improved by 2.7% in a group treated with heparin and 6.2% in the urokinase group but both groups were equal in perfusion by day five. A recent trial showed that patients with right ventricular dysfunction failed to show an improvement in death rates. Many patients with pulmonary embolism are poor candidates for lytic therapy due to recent surgery or other reasons. There are reports of lytic therapy leading to sudden death from pulmonary embolism due to lysis of large leg thrombi. Also of concern is the 1-2% risk of intracranial hemorrhage which accompanies thrombolytic therapy.

The vast majority of patients with pulmonary embolism who survive long enough to be diagnosed will survive. Therefore only a small number of patients would benefit from thrombolytic therapy. However, for the patient in extremis due to a pulmonary embolism who is not a candidate for embolectomy, fibrinolytic therapy is an option.

If thrombolytic therapy is required, the dosing for the agents is the same as for cardiac indications. Plasma fibrinogen and aPTT should be measured every four hours after treatment. When the aPTT is below two times normal and the fibrinogen is over 100 mg/dl, heparin should be started.

Thrombolytic therapy for deep venous thrombosis has little effect on long-term outcomes such as post-phlebitic syndrome. It therefore has little role in management of these patients. One place where lytic therapy may be useful is in massive deep venous thrombosis involving the common femoral or iliac system. One approach is to use catheter guided lytic therapy to recanalize the vessel. Typically this is done when the vein does not spontaneously recanalize and the patient has severe and persistent symptoms.

Embolectomy may be useful in the small subset of patients who are in unresponsive shock. Some series claim up to 70% survival. It has been suggested that if after an hour of medical management, a patient has persistent signs of massive PE such as a systolic blood pressure of less than 90 mmHG, urine output of less 20 ml per hour and/or PO_2 of less than 60 mmHg, that patient is a candidate for embolectomy. This approach obviously requires the presence of a qualified cardiac surgeon.

Vena cava filter—The role of filters in treatment of thromboembolic disease is unclear due to lack of good trials. A strong indication for filter placement would be pulmonary embolism/deep venous thrombosis in a patient in whom anticoagulant therapy is contraindicated. A trial showed that patients at high risk for pulmonary embolism who were treated with heparin had fewer pulmonary emboli with filter placement. This trial did not demonstrate any improvement in survival with filter placement. Some people have used filters as prophylaxis in patients unable to be anticoagulated. The role of filters in long-term prevention is unknown. The risk of deep venous thrombosis is doubled with long-term filter placement. It is unclear if patients with filters require lifelong anticoagulation. The disadvantages of filters are leg edema from filter thrombosis, no protection against thrombosis, and venous collateral formation years after filter placement. Recently a trend toward widespread clinical use of removable IVC filters has been seen, and these may prove to be useful for patients who transiently cannot be anticoagulated or who are at high risk for thrombosis and need surgery.

Compression stockings are extremely useful in the prevention of post-phlebitic syndrome. A recent randomized trial demonstrated halving the rate of post-phlebitic syndrome with compression stocking use. Patients should be advised that they should wear stockings most of the day, everyday for best effect.

Treatment of Deep Venous Thrombosis

There is now abundant evidence that use of low molecular weight heparin (LMWH) for therapy in DVT/PE treatment is both safer and more effective than use of standard heparin. Evidence is also clear that stable patients with DVT/PE can be treated at home with LMW heparin. There are two low molecular weight heparins (LMW heparin) approved for therapy, enoxaparin 1mg/kg every 12 hours or tinzaparin 175 units/kg every day. For patients with low thrombotic burden one may use enoxaparin 1.5 mg/kg every day. For short courses of therapy most patients

do not need to have LMW heparin levels drawn. Patients who are very obese (greater than two times ideal body weight), pregnant, those with severe liver or heart failure, or those on long-term heparin therapy should have levels performed. In patients with renal failure dosing should be once per day. Levels are drawn four hours after injection and the therapeutic range for enoxaparin is 0.7-1.2 anti-Xa units.

These regimens may be used with either inpatients or outpatients. Although LMW heparin is more expensive than standard heparin, inpatient savings can be realized since multiple aPTT's or platelet counts are unnecessary. In addition, in inpatient populations the early trials demonstrated that LMW heparin was more effective and safe than standard heparin.

The ability to give LMW heparin subcutaneously has opened the door to outpatient therapy. Careful patient selection is crucial. A patient should be considered for outpatient therapy if the only thing that would lead to their admission was administration of intravenous heparin. The first dose of LMW heparin is given as soon as possible, and warfarin is started the first evening of diagnosis. The second dose of LMWH should be a "transition" to get the patient on an 8 am & 8 pm schedule. This is derived by adjusting the second dose of LMW heparin for the difference between the first and second dose. This is done by multiplying the patient's usual dose of 1mg/kg by the difference in time between the first two doses divided by 12. For example, if a 60 kg patient received his first dose at midnight, at 8 am the patient would get 40 mg and from then on 60 mg every 12 hours. Patients should be followed every day with a visit or phone check. One still needs to overlap LMW heparin and warfarin by 24 hours once the INR is in the therapeutic range.

As discussed in more detail in Chapter 22, standard heparin is fading from use due to its unfavorable pharmacokinetics and the demonstration of better outcomes with LMWH. If used, the absolute key in standard heparin use is to give enough. The standard bolus should be 5,000 units (10,000 for larger thrombi or pulmonary embolism). The initial drip should be 1400 units/hr. The aPTT should be checked 6 hours after the bolus and the drip adjusted accordingly. A supratherapeutic aPTT may just reflect the bolus. The drip should never be turned down until two consecutive aPTT's are supratherapeutic. Therapeutic range varies with different aPTT reagents and must be standardized at each laboratory with heparin levels. One must be very aggressive in rapidly achieving the proper aPTT.

All patients should receive at least five days of heparin therapy. Some authorities recommend that ten days of heparin should be given for large PE since it has not been proven that five days is sufficient therapy.

Warfarin is started the evening of diagnosis (or day five of therapy if ten days of heparin is being used) with a loading dose of 2.5-10 mg orally. Five mg is recommended in most patients. Young (under age 60) healthy patients may need a 10 mg loading dose while the frail elderly (over age 85) should start with 2.5 mg. Warfarin is titrated to an INR of 2-3. Use of warfarin affects all the vitamin K dependent proteins. Factor VII falls first, resulting in prolongation of the INR. However, the full antithrombotic effect of warfarin does not occur until factors X and II have fallen. This fall will take an additional 24 to 48 hours after factor VII levels fall. This is why patients should overlap heparin and warfarin therapy for several days.

Recently, it has been reported that the direct thrombin inhibitor ximelagatran in the dose of 36 mg twice a day can be used instead of heparin/warfarin in therapy of DVT/PE. Ximelagatran offers the advantage of more predicable dosing and lack of drug interactions. This agent is described in more detail in Chapter 23.

Special Situations

Patients with Cancer

The hypercoagulable state associated with malignancy (especially adenocarcinomas) can be refractory to warfarin therapy. Long-term LMW heparin is a useful alternative in these patients. Patients should have LMW heparin levels checked weekly until the dose is stable. Very rare patients may have tumors which secrete heparinases. These patients may require higher doses of heparin. Recent clinical trials suggest that any patient with a diagnosis of cancer may benefit from being treated for the full six month course with just LMW heparin. Cancer patients treated with LMW heparin has significantly lower rates of recurrent thrombosis.

Pregnant Patients

This is discussed in Chapter 28.

Patients with Antiphospholipid Antibody Syndrome

Although it was thought that these patient require warfarin at an INR of 3.0-3.5 to prevent breakthrough thrombosis a prospective trials has shown that a target range of 2.0-3.0 is adequate for most patients. Patients who break through warfarin require long-term LMWH because it is insufficient therapy just to raise the INR target range.

Calf Vein Thrombosis

Patients with calf vein thrombosis are at risk for extension to proximal vein thrombosis and subsequent pulmonary embolism. These patients should be anticoagulated with a heparin and then with warfarin for 6 weeks. Patients with thrombosis in the muscular veins of the calf (soleal, gastrocnemial) can be treated just with 10 days of therapeutic LMWH or, if stable, simply observed with serial ultrasounds.

Superficial Venous Thrombosis

Most superficial venous thrombosis can be treated with heat and anti-inflammatory agents. However, 20-30% of patients with greater saphenous vein thrombosis will go on to have thrombosis of the deep system. These patients may be treated with a short course of heparin or monitored with serial ultrasounds. Data has been presented showing that a ten day course of enoxaparin 40 mg/day is effective at both reducing symptoms and preventing progression and should be considered for very proximal saphenous vein thrombosis or for very symptomatic superficial thrombosis.

Duration of Therapy

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The keys questions to consider when determining duration of therapy is 1) what was the location of the thrombosis, 2)what were the circumstances of the thrombosis, and 3) are there any underlying hypercoagulable states?

Patients with thrombosis in unusual sites such as cerebral vein thrombosis or portal vein thrombosis should be indefinitely anticoagulated. An exception would be if there was a clear provoking factor such as an abdominal abscess leading to portal vein thrombosis. In these cases six months of therapy would be prudent. Also as discussed in the next chapter, upper extremity thrombosis need just limited therapy.

An important factor in determining risk of recurrence is assessing whether the thrombosis was idiopathic or provoked. Most studies indicate for a patient to be considered to have an idiopathic thrombosis they should not have cancer, not have undergone surgery or had trauma in the previous six weeks, not been at bedrest, not

be pregnant, or have a major hypercoagulable state. Patients with idiopathic venous thrombosis are at substantial risk of recurrence with a risk that may be as high as 30% in the next five years. Three studies have indicated that long term anticoagulation therapy is of benefit in these patients in preventing recurrent thrombosis. Patients with idiopathic thrombosis, especially large thrombosis or pulmonary embolism, should be considered for indefinite anticoagulation. Trial data does show that warfarin at an INR of 2-3 is just as safe and more effective than 1.5-2 and this should be the therapeutic range for these patients. Most patients with a provoked first proximal deep venous thrombosis and no underlying hypercoagulable state should be anticoagulated for six months.

Patients with first thrombosis and "strong" hypercoagulable states (antiphospholipid disease, antithrombin III, protein C or protein S deficiency) should receive life-long anticoagulation. Patients with a "weak" hypercoagulable state (factor V Leiden, etc..) and a removable risk factor can be anticoagulated for just six months. However, patients with two or more weak states or a severe idiopathic thrombosis should be considered for indefinite anticoagulation.

Prophylaxis

Overview

Etiology of surgical hypercoagulable states—The etiology of the surgically induced hypercoagulable state is complex. Certainly venous stasis during and after the operation is important. The surgery-induced inflammatory state will cause pro-coagulant changes in the blood and vessel endothelium. Direct venous trauma in orthopedic and pelvic surgery plays a role. Patients with a pre-existing hypercoagulable state (acquired or inherited), previous venous thrombosis, heart failure, malignancy, or estrogen use are at higher risk for thromboembolic disease in the operative period. Smokers have an increased risk as well.

The need for deep venous thrombosis prophylaxis in surgery—The first sign of thrombosis in 10-30% of patients is sudden death. The clinical signs of deep venous thrombosis tend to be unreliable. In most large screening studies only 10-20% of patients with deep venous thrombosis are symptomatic. Prevention is crucial, not only to prevent DVT/PE but because up to 90% of patients with deep venous thrombosis will experience post-phlebitic syndrome. This included patients with asymptomatic thrombosis. Finally, it is better to prevent deep venous thrombosis since treatment in the post-operative period is associated with a higher risk of bleeding. Numerous studies have shown deep venous thrombosis prophylaxis to be medically sound as well as cost-effective. Failure of surgeons to use deep venous thrombosis prophylaxis is the largest cause of preventable operative death in the United States.

Who Is at Risk?

Low Risk Patients

- Patients under 40 with no other risk factors (including *negative* family history of deep venous thrombosis).
- Procedures lasting less than 30 minutes.

Medium Risk Patients

- Patients over 40 years of age with no other risk factors undergoing operations over 30 minutes long.

High Risk Patients

- Previous history of venous thrombosis (or strong family history).
- Pelvic or abdominal surgery for malignancy. Lower limb orthopedic surgery.

Very High Risk Patients

- Lower limb trauma and surgery.
- Surgery in patients with other risk factors-previous pulmonary embolism, CHF, cancer.

The Treatment Regimens

Pneumatic Booties (Intermittent Pneumatic Compression)

Mechanical means of preventing deep venous thrombosis by squeezing calves. Compression also stimulates fibrinolysis. Disadvantages of compression include patient discomfort, noncompliance, and risk of mechanical breakdown. Compression is effective in medium and some high risk patients. The newer devices stimulating only the foot appear to be equivalent in effectiveness to the more complex leg device but have not been as extensively studied.

Subcutaneous Heparin

The standard (5,000 units TID) prophylactic regimen. The dose is started 2-8 hours before surgery and given until the patient is ambulatory. Low dose-heparin is effective in medium but not high-risk patients. Bleeding increases from 3.8% in placebo patients to 5.9% in patients receiving heparin when all studies are considered, but this is far outweighed by prevention of both thrombosis and death.

Aspirin

Studies using aspirin have not consistently shown that aspirin prevents deep venous thromboses. In all the NIH/ACCP consensus statements, aspirin is not considered a choice for deep venous thrombosis prophylaxis. Unlike heparin and warfarin, aspirin's antithrombotic effects are not reversible. Of additional concern is aspirin's gastrointestinal toxicity and prolonged inhibition of platelet function. Recently a large randomized trial demonstrated that aspirin was ineffective at preventing DVT/PE in patients undergoing total hip replacement and was associated with more bleeding.

Warfarin

There are several regimens for warfarin in the literature. The "two step" approach gives low doses of warfarin for 1-2 weeks before the operation to raise PT to 1.5-3 (INR 1.5) seconds above control. Post-op the warfarin dose is increased to raise the INR to 2-3. This approach is particularly effective in preventing deep venous thrombosis after elective hip or knee replacement. This is effective in high-risk patients with only a 4% incidence of post-op bleeding. The other approach is to give 5 mg of warfarin daily starting immediately after surgery (or in some studies the night before) to achieve an INR of 2.0-3.0 as soon as possible after surgery. Anticoagulation is continued for three-six weeks. This was effective in reducing deep venous thrombosis after surgery for hip fractures. The prothrombin time/INR should be followed to monitor the patient's status and prevent overshooting of the INR. Rates of bleeding

are as high as 30%, but most bleeding is seen in patients who are over-anticoagulated. In more recent studies where therapy is closely monitored, significant post-op bleeding was not a problem.

Low Molecular Weight Heparin

Low molecular weight heparin is equal to or better than warfarin or adjusted-dose subcutaneous heparin for high risk patients. Low molecular weight heparin can also be given once a day in lower risk patients and has a lower incidence of heparin-induced thrombocytopenia.

Fondaparinux

This agent is a synthetic pentasaccharide which binds to antithrombin. It is approved for use in DVT prevention with hip and knee replacement. It is renally cleared and should not be used in patients with renal insufficiency. Also, given the fixed dose (2.5 mg), it should not be used in patients weighing under 50 kilograms. The relative effectiveness of this agent vs LMWH is still controversial.

Ximelagatran

This is an orally available thrombin inhibitor. Studies in lower extremity orthopedic surgery has shown it to be effective in DVT prevention for hip and knee surgery. Currently dosing is 24 mg po twice a day.

The Situations

Low Risk Patients

Patients under 40 and with no other risk factors (including a negative family history of deep venous thrombosis) or patients undergoing procedures less then 30 minutes long do not need prophylaxis.

Medium Risk Patients

Patients over 40 years of age undergoing operations over 30 minutes long and with no other risk factors should receive low dose heparin. Heparin, 5,000 units TID, is started 2-8 hours before surgery and given until the patient is ambulatory. Compression stockings or LMW heparin (dalteparin 2500 - 5000 units every day or enoxaparin 40 mg/day) are also effective. Low molecular weight heparin should be considered in patients undergoing surgery for abdominal cancers given their high risk of thrombosis.

High Risk (Non-orthopedic) Patients

Previous history of venous thrombosis (or strong family history of thrombosis) or pelvic or abdominal surgery for malignancy puts a patient in a high-risk category. Low-dose heparin has been shown to be less effective in patients with previous thrombosis and malignancies (especially gynecological). In patients with a thrombotic history, use of one of the low-dose warfarin regimens or an aggressive LMW heparin regimen (i.e., enoxaparin 30 mg q12 hours) is effective. Pneumatic booties have been shown to be effective in patients with gynecological malignancies. Patients with very recent deep venous thrombosis, who are ill, and who absolutely need surgery require LMW heparin along consideration of a temporary IVC filter.

Knee Surgery

High incidence of calf vein deep venous thrombosis (60%) but low incidence of pulmonary embolism accompanies knee surgery. LMW heparins, fondaparinux, and ximelagatran has been shown to be the most effective for deep venous thrombosis prevention. There is a high incidence of pulmonary embolism in bilateral knee surgery.

Elective Hip Surgery

In patients undergoing elective hip surgery there is a high incidence of deep venous thrombosis (50%), pulmonary embolism (11%) and fatal pulmonary embolism (2%). Low-dose heparin and aspirin are not effective in this situation. Although pneumatic booties are effective for prophylaxis, they have been recently shown to be inferior to two-step warfarin therapy. Effective in all patients are one of the warfarin regimens, adjusted dose heparin, LMW heparin, fondaparinux, or ximelagatran. Prophylaxis is most effective if started before the operation or (with LMW heparin) the same day as the surgery. In patients with other risk factors for deep venous thrombosis, prophylaxis should be extended to 3-4 weeks after the surgery since 20-25% of deep venous thrombosis happen after the first week post-op. Recent trials have shown benefit with the extended use of LMW heparin post-operatively in all risk groups of patients.

Hip Fractures

This is the highest risk situation. Risk of deep venous thrombosis is 50-80%; risk of pulmonary embolism is 11-20%; and risk of fatal pulmonary embolism 5-7%. Again, low-dose heparin and aspirin are not effective in this situation. Warfarin has been studied for over 30 years and had been found to be effective in reducing the risk of pulmonary embolism from 5-7% to 1%. Thus for every 2-6 patients who have a wound hematoma one patient's life will be saved. LMW heparin and fondaparinux are also very effective in these patients. The situation of the hip fracture patient is complicated by the fact that as many as 10% of patients have deep venous thrombosis before any hip surgery.

Trauma

These patients are at high risk not only for thromboembolic complications but also for bleeding. Once patients are stable (and if they do not have intracranial hemorrhage) enoxaparin 30 mg every 12 hours should be used. For patients with ongoing bleeding pneumatic stockings and IVC filter may be of some benefit. Patients with spinal cord injury are at high risk for thrombosis and should receive low molecular weight heparin.

Neurosurgery

Patients are at risk for thrombosis but until recently pharmacologic prophylaxis was not used due to fear of bleeding. However, a recent study indicated that enoxaparin 40 mg/day was more effective than pneumatic stockings with no associated higher incidence of bleeding. Patients undergoing neurosurgery for brain tumors are at particular risk of thrombosis and should receive LMW heparin.

Medical Patients

Medical patients are at risk for deep venous thrombosis. The range is from 20% in patients with heart failure or pneumonia to as high as 80% in stroke patients. The risk of deep venous thrombosis is increased in patients who smoke, have heart failure, cancer, and previous venous thrombosis. Studies involving thousands of medical patients have shown that low-dose heparin is effective for prophylaxis of venous thrombosis. It reduces deep venous thrombosis by 66%, pulmonary emboli by 50% and fatal pulmonary embolism by 0.5%. Pneumatic booties may also be effective in these situations. Recent clinical trials have shown that LMW heparins are equal or superior to standard heparin for prophylaxis of the high-risk medical patient.

Patients over 40 and those with serious illnesses, especially heart failure and pneumonia, benefit from low-dose heparin. ICU patients should receive LMWH due to the high incidence of deep venous thrombosis in this population. Patients with strokes are at high risk for deep venous thrombosis and consideration should be given to pneumatic booties plus low-dose heparin or LMW heparin.

In Pregnancy

Most experience is with enoxaparin 40 mg every day or with daltaparin 5000 units every 12-24 hours. See Chapter 28 for more details.

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CHAPTER 16

Thrombosis in Unusual Sites

Although the venous system is present throughout the body, the vast majority of thrombosis occurs in the deep veins of the legs. Thrombosis can occur in other locations and when it does is often a marker of underlying pathology.

Upper Extremity Thrombosis

Thrombosis of the upper extremity occurs commonly in two situations. The first is in the presence of a venous catheter. As discussed more thoroughly in Chapter 27, thrombosis is a common problem with long-term venous catheters.

The second aggravating situation occurs with exertion. Vigorous use of the arm in such actions as throwing can compress the subclavian vein and result in thrombosis. Patients will note arm pain and swelling soon after the activity but ascribe it to muscle pain. These patients may have anatomic variants such as thoracic outlet syndrome which predispose them to thrombosis.

Despite its frequent occurrence in young people, the incidence of classic hypercoagulable states in patients with upper extremity thrombosis is not higher than that of the normal population. This is consistent with the idea that most of these thromboses are due to mechanical factors.

Therapy of upper extremity thrombosis is with anticoagulation to prevent clot extension and pulmonary embolism. The ideal duration of anticoagulation is unknown, but 4-6 weeks is reasonable for catheter-related thrombosis given that the provocation for the thrombosis has been removed. The limited data available suggests that patients with exertion-related thrombosis should receive 3 months of therapy. Patients with upper extremity thrombosis often do not recanalize the vein but will form extensive collaterals. Some patients will have persistent, severe swelling and pain after thrombosis. This has led some to advocate thrombolytic therapy of any upper extremity thrombosis. As any use of systemic thrombolytic therapy carries with it a 1% risk of intracranial hemorrhage, any potential benefit must be weighed against this risk. Catheter-directed thrombolytic therapy should be considered for any patient with severe arm swelling, especially young patients with exertion- related thrombosis. Most (but not all) studies suggest a benefit in clinical outcome with thrombolytic therapy but this has never been prospectively studied. Rare patients, especially those with recurrent vascular compromise on arm raising, may benefit from first rib resection.

Cerebral Vein Thrombosis

Cerebral vein thrombosis commonly occurs in the cerebral sinuses, but some cases will occur in the deep cerebral veins. Risk factors for thrombosis include the presence of venous hypercoagulable states. Patients with acquired hypercoagulable states such as Beçhet's disease appear to be at increased risk. Another group of patents at risk are those suffering from severe dehydration with "sludging" of the cere-

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

bral blood flow. Finally, patients may have thrombosis due to local irritation of the venous sinuses. The classic presentation of infection-related thrombosis is cerebral vein thrombosis due to irritation of the transverse sinus by mastoiditis, so-called "otic hydrocephalus."

Patients with cerebral vein thrombosis can present with one of two major patterns. The first is with focal neurologic defects due to venous thrombosis resulting in localized infarction. Infarctions are often hemorrhagic due to continued arterial blood flow, which pumps blood into the infarcted area. Patients with deep cerebral vein thrombosis may present with severe deficits and coma due to infarction of deep brain structures. Secondly and more commonly, patients with cerebral vein thrombosis will present first with signs of increased intracranial pressure due to obstruction of venous flow and cerebral spinal fluid reabsorption. Patients will have severe headaches, nausea and vomiting and then may progress to coma. Patients may also have reduced vision and blindness due to pressure on the optic nerve. Frequently patients have a prolonged course lasting for days with gradual worsening of symptoms.

Especially early in the course of cerebral vein thrombosis, patients may present with non-specific signs and symptoms. Often patients may be misdiagnosed as having pseudotumor cerebri. This occurs if only CT scanning is done and found to be normal and the lumbar puncture shows high opening pressures. Diagnosis of cerebral vein thrombosis is best made by MRI and MR angiography which best show the venous obstruction.

Cerebral vein thrombosis requires anticoagulation. Despite the frequent presence of hemorrhagic transformation, immediate heparin therapy is associated with an improvement in outcome. In the Einhaupl trial, when patients received a small 3,000 unit bolus and were anticoagulated with standard heparin, a dramatic improvement in outcome was seen compared to controls. Patients with severe neurological deficits may benefit from angiography and direct thrombolytic therapy of the venous obstruction. Patients with provoking factors such as ear infection or other local infections should be anticoagulated for six months. Patients with underlying hypercoagulable states should be anticoagulated indefinitely.

Adrenal Infarction

The adrenal gland contains a plexus of small veins and venules which receive the secreted hormones of the adrenal gland. This venous structure appears prone to thrombosis in several hypercoagulable states. Patients with purpura fulminans may present with adrenal crisis due to thrombosis and the resultant hemorrhagic destruction of the gland. Patients with heparin- induced thrombocytopenia may rarely infarct the gland and have subsequent hemorrhage. Finally, patients with antiphospholipid antibody syndrome can have adrenal infarctions. The presentation in APLA patients is often one of adrenal insufficiency that initially may be overlooked due to nonspecific symptoms.

Budd-Chiari Syndrome

Patients with Budd-Chiari syndrome or hepatic vein thrombosis present with the onset of a painful swollen liver and ascites and may progress to liver failure. Several hypercoagulable states are associated with Budd-Chiari syndrome (Table 16.1). These are myeloproliferative syndromes, antiphospholipid antibodies, paroxysmal nocturnal hemoglobinuria, and Beçhet's disease. Budd-Chiari may be the presenting sign of a myeloproliferative syndrome and can occur with normal blood counts. This presentation is discussed further in Chapter 27.

Table 16.1. Hypercoagulable states associated with Budd-Chiari syndrome and portal vein thrombosis

- Antiphospholipid antibodies
- Beçhet's disease
- Myeloproliferative syndrome
- Paroxysmal nocturnal hemoglobinuria

Therapy is partially dictated by the severity of the liver disease. Since these patients have a hypercoagulable state and are at risk for further life-threatening thrombosis, anticoagulation should be initiated at the time of diagnosis of the thrombosis. Patients who present acutely may be treated with catheter-guided thrombolytic therapy. Patients who present with chronic obstruction may benefit from either surgical or catheter-placed shunts. Patients with hepatic vein thrombosis due to myeloproliferative syndromes do poorly with surgery; therefore, catheter-based shunt approaches should be tried first. Despite the presence of hypercoagulable states, if the patient is anticoagulated shunt thrombosis is uncommon. Patients who undergo liver transplantation and have an identifiable hypercoagulable state should be aggressively anticoagulated to prevent thrombosis of the liver graft.

Portal Vein Thrombosis

Portal vein thrombosis can occur either as a complication of local inflammation or be a sigh of hypercoagulable states. Local factors associated with portal vein thrombosis include abdominal abscess, inflammatory bowel disease, or tumor compression. Portal vein thrombosis can also be a complication of surgery, especially splenectomy in patients with myeloproliferative disorders. Like Budd-Chiari syndrome, portal vein thrombosis can also be a complication of hypercoagulable states including the unusual ones listed in Table 16.1.

Therapy of portal vein thrombosis is aggressive anticoagulation. Patients with post-surgical thrombosis can recanalize with anticoagulation. Patients benefit also from long term anticoagulation. Data shows that patients with portal vein thrombosis who are anticoagulant do not have higher rates of bleeding but do have reduced rates of thrombosis.

Renal Vein Thrombosis

Renal vein thrombosis most often accompanies nephrotic syndrome. It is also associated with malignancy but is less often seen with the inherited hypercoagulable states. Patients can present with a clinical spectrum ranging from sudden onset of severe flank pain to a subtle deterioration of renal function. Patients with pre-existing renal disease may simply present with worsening renal function. Total venous occlusion will result in hemorrhagic infarction of the entire kidney. Acute thrombosis resulting in renal impairment can be treated with catheter-guided thrombolytic therapy. Patients with more chronic presentations require long-term anticoagulation.

Visceral Vein Thrombosis

Deep venous thrombosis and cerebral vein thrombosis are the two most common presentations of hypercoagulable states. The mesenteric veins are the third most common presenting site. Patients usually present with abdominal pain out of

Table 16.2. Priapism

High Flow: Increased arterial blood flow to penis
Low Flow: Obstruction of venous drainage
- Sickle cell disease
- DIC with thrombosis
- Venous trauma
- Tumor infiltration
- Medications

Diagnostic Approach
- Doppler ultrasound of vasculature
- Aspiration of corporeal blood for blood gas analysis:
  - pH less than 7.25 and oxygen less than 30 mmHg suggestive of low flow state

Treatment of Low-Flow Priapism
- Corporeal aspiration of 60 ml of blood and injection of 200 μg of phenylephrine
  - Repeat for a Total of Three Injections (if needed)
  - If this fails patients should undergo Corporo-Spongiosum shunting
- Patients with sickle cell disease should undergo exchange transfusion first to lower percentage of sickle cells to under 30%

proportion to physical findings. Diagnosis can be established at the time of surgery or with CT scanning showing thrombus in the mesenteric vein. Patients may suffer extensive bowel infarction with mesenteric vein thrombosis. Patients with mesenteric vein thrombosis should be treated indefinitely with anticoagulation, even in the absence of an identifiable hypercoagulable state, because this condition has a strong association with recurrent thrombosis.

Retinal Vein Thrombosis

Retinal vein thrombosis is a not-uncommon cause of impaired vision. Despite the venous infarction, patients with retinal vein thrombosis do not appear to have a higher incidence of underlying hypercoagulable states. Instead, risk factors for arterial disease are often present. The retinal artery and vein share the same sheath in the eye and a rigid atherosclerotic artery may predispose to compression of the vein. Patients with branch retinal vein thrombosis also tend to have the artery overlying the vein at the site of thrombosis. This gives further credence to the idea that local compression instigates thrombosis. Patients with retinal vein thrombosis should not be treated with anticoagulation as this may provoke retinal hemorrhage.

Priapism (Table 16.2)

Priapism is caused by one of two underlying mechanisms. The first is high-flow priapism due to increased arterial blood flow to the cavernosa. The penis is infused with well-oxygenated blood and permanent damage is not seen. This is most often seen with traumatic arterial-venous shunts.

Low-flow priapism results from blockage of the venous drainage of the cavernosa. This leads to hypoxia and ischemia of the cavernosa and is an emergency. Patient may have low flow priapism due to sickle cell disease, DIC with thrombosis, venous trauma, tumor infiltrations, or from medications such as trazodone or ecstasy.

Usually the history is helpful in differentiating low vs high flow priapism. If the cause is uncertain, patients can have doppler ultrasound of the vasculature. High

blood flows are suggestive of high flow priapism. Another useful test is aspiration of corporeal blood with blood gas analysis. A pH of less that 7.25 and an oxygen level under 30 mmHG is diagnostic of a low-flow state.

Patients who present with low-flow priapism should undergo corporeal aspiration of 60 mL of blood and injection of 200 μg of phenylephrine. The phenylephrine can be repeated for a total of three injections. If this fails, patients should undergo corporo-spongiosum shunting.

Patients with priapism due to sickle cell disease should undergo exchange transfusion to reduce the percentage of sickle cells to under 30%. If this is unsuccessful, then corporeal aspiration of 60 mL of blood and injection of 200 μg of phenylephrine can be tried, but this is rarely successful in sickle cell patients. Patients who fail therapy will require a corporo-spongiosum shunt.

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CHAPTER 17

Hypercoagulable States

A hypercoagulable state is defined as a condition in which, due to an inherited or acquired disorder, there is a propensity to form thrombosis. This hypercoagulability is manifested clinically by either a greater number of thromboses, thrombosis at an early age, a familial tendency toward thrombosis, or thrombosis at unusual sites. The fundamental approach is to decide whether a hypercoagulable state is present by the logical ordering and interpretation of tests, and then if the patient has a hypercoagulable state, to decide on appropriate therapy.

When to Suspect a Hypercoagulable State (Table 17.1)

A hypercoagulable state is manifested clinically by:

1. **Thrombosis at an early age**. It is uncertain what age limit should be used for this criterion. Thrombosis in patients with inherited hypercoagulable states often starts in the teenage years. Despite the predilection for thrombosis early in life, the risk of thrombosis in patients with hypercoagulable states increases as the patient gets older. The Physician's Health Study showed a relative risk of thrombosis in carriers of Factor V Leiden of 2 in patients less than 60 and 7 in patients more than 60. An arbitrary age cutoff of 50 has been suggested, but older patients who have spontaneous thrombosis and a suggestive family history should also be evaluated for inherited hypercoagulable states.
2. **Familial tendency toward thrombosis**. The penetrance of hypercoagulable states is variable. Lack of a family history of thrombosis should not deter one from evaluating a patient.
3. Thrombosis at **unusual sites** such as the cerebral or mesenteric veins. As noted in Chapter 16, upper extremity thrombosis is usually due to mechanical causes and should not provoke an evaluation for hypercoagulable states.
4. **Recurrent thromboses**—especially if they are idiopathic.

Table 17.1. Markers of hypercoagulable states

- Thrombosis at early age
- Family history of thrombosis
- Thrombosis at unusual site
- Multiple thromboses

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

Why Diagnose Hypercoagulable States?

Some people question the utility of diagnosing a specific hypercoagulable state given that the therapy (long-term anticoagulation) is often the same. However, several arguments can be made for diagnosing the exact hypercoagulable state(s). One is that the duration of anticoagulation may vary. Secondly, the therapy may vary. In patients without a hypercoagulable state, limited anticoagulation is usually indicated, but the diagnosis of a hypercoagulable state mandates the need for lifelong anticoagulation due to the risk for recurrent thrombosis. Patients with antithrombin III deficiency will require concentrates during high-risk situations such as surgery. The final reason for screening patients for inherited hypercoagulable states is that family screening is of value. The risk of first thrombosis is higher in affected relatives, and with predictable additional stressors such as pregnancy, prophylactic measures can be taken.

Approach to the Patient Suspected of Having a Hypercoagulable State

Unfortunately (unlike with bleeding disorders) no screening tests for hypercoagulable states are available. The clinical setting should guide ordering a rational evaluation. When evaluating a patient one should ask the following questions:

Is the Thrombosis Arterial or Venous?

A critical piece in planning the evaluation is determining whether the thrombosis is arterial or venous. Most hypercoagulable states manifest themselves as predominantly venous thrombosis. Although anecdotal reports of arterial thrombosis associated with protein C, protein S, and antithrombin III deficiency exist, reviews of large patient cohorts have not proved an association. Arterial thrombosis is primarily either associated with atherosclerosis or embolism and not with the "classic" hypercoagulable states.

Where Is the Site of Thrombosis?

Although many hypercoagulable states present with deep venous thrombosis, certain hypercoagulable states have a predilection for visceral thrombosis. Myeloproliferative syndromes, paroxysmal nocturnal hemoglobinuria, and Behcet's disease are strongly associated with visceral thrombosis. Conversely, thrombosis of the upper extremity is rarely associated with a hypercoagulable state.

What Is the Age of Patient?

Unlike the inherited bleeding disorders, hypercoagulable states rarely present with thrombosis during the childhood years. Patients with inherited hypercoagulable states often have a first thrombosis in the late teens to thirties. A sudden onset of thrombosis in older patients raises the specter of neoplasm or of an acquired hypercoagulable state.

Were There Any Associated Risk Factors for Thrombosis?

The suspicion of a hypercoagulable state needs to be tempered by the situation in which the thrombosis occurred. Thrombosis in older patients after surgery or during hospitalization is common and not necessarily a sign of a hypercoagulable state. In the younger patient, thrombosis with a thrombotic stressor may be the first sign of an underlying hypercoagulable state. For example, 60-70% pregnant women

with thrombosis will have an identifiable hypercoagulable state upon evaluation. Young patients who have thrombosis, even with other risk factors, should be screened for coagulation defects.

Is There a Family History of Thrombosis?

Since many hypercoagulable states are inherited, determining a family history of thrombosis is crucial. The thrombotic tendency has a variable penetrance and therefore the rate of thrombosis may be considerably lower than the 50% expected from an autosomal dominant trait. Thus, a detailed family history should be obtained.

Screening Family Members

Limited data now exists to suggest that asymptomatic carriers of inherited hypercoagulable states are also at up to 10% risk for thrombosis with stressors such as pregnancy or surgery. Thus, blood relatives of patients with inherited hypercoagulable states should be screened and offered prophylaxis before surgery and in other high-risk situations.

The Congenital Hypercoagulable States (Table 17.2)

Factor V leiden (hereditary resistance to activated protein C [HRAPC]) is a defect in factor V which renders it unable to be degraded by activated protein C. Factor V Leiden is associated with venous thrombosis. This mutation is very common: it comprises 40 - 60% of hypercoagulable states, 20% of first DVTs, and is found in 2 - 8% of the normal population. It is estimated that the presence of factor V Leiden is associated with an increased relative risk of thrombosis of 3 fold.

Prothrombin gene mutation is a defect in the prothrombin gene (nt20210 G→A). The pathophysiology of its hypercoagulable state is unknown but may be due to elevated levels of plasma prothrombin. The prothrombin gene mutation is present in 1-2% of the normal population but is seen in perhaps 10-20% of patients with hypercoagulable states. Like Factor V Leiden it is associated with venous thrombosis and increases the relative risk of thrombosis 3 fold. Patient who have both factor V Leiden and the prothrombin gene mutation have a markedly increased risk of thrombosis.

Protein C is a protein which, when activated by thrombin, degrades factors V and VIII. Deficiency of protein C primarily causes venous thrombosis. The relative risk of thrombosis in those with protein C deficiency is estimated to be 10, while the risk in carriers ranges from 0.5 - 2.5%/year.

Table 17.2. Inhertied hypercoagulable states

Defect	Incidence in Population	Percent of Hypercoagulable States	Relative Risk of Thrombosis
Factor V leiden	2-8%	40-60%	3
Prothrombin gene mutation	1-2%	10%	3
Protein C deficiency	1:200	5-10%	10
Protein S deficiency	1:2-5,000	5-10%	10
Antithrombin III deficiency	1:2-5,000	1-3%	10
Dysfibrinogenemia	Rare	1	?

Protein S is a cofactor for Protein C. Protein S exists both in bound and unbound form. Deficiencies of total protein S and of unbound protein S (more common) can lead to a hypercoagulable state. Like protein C deficiency, the risk of thrombosis is increased ten fold, with the risk for carriers 0.9- 3.5%/year. Protein S deficiency primarily causes venous thrombosis.

Antithrombin inhibits activated clotting factors. Deficiency of antithrombin primarily causes venous thrombosis and may increase the risk of thrombosis up to 30 fold. Lack of antithrombin is usually not associated with heparin resistance.

Dysfibrinogenemia is a state in which defective fibrinogen molecules form clots which are difficult to degrade by fibrinolytic agents. Dysfibrinogenemia can be associated with both venous and arterial thrombosis. Due to the difficulty with thrombus formation, some patients with dysfibrinogenemia may also have a bleeding diathesis.

Factor VIII There is now convincing evidence implicating high levels of factor VIII (>150%) in venous thrombosis with a relative risk of 3 and high risk of recurrence. Mechanism of the factor VIII elevation is unknown but may be a combination of genetic factors and acquired risk factors such as inflammation.

Lipoprotein (a) is a lipoprotein with uncertain function. High levels of lipoprotein(a) increase the risk of arteriosclerosis. The role of high levels of lipoprotein(a) in venous thrombosis remains controversial.

Fibrinolytic disorders in theory should be classic causes of hypercoagulable states. However, the role of defects in fibrinolytic enzymes in congenital hypercoagulable states is controversial. No convincing relationship has been shown between defects in fibrinolysis and inherited hypercoagulable states.

Suggested Evaluation in Patients with Venous Thrombosis

The patient with venous thrombosis suspected of having a hypercoagulable state should be screened for diseases listed in Table 17.3.

Table 17.3. Evaluation of patients with hypercoagulable states

- Activated protein C resistance ratio (factor V Leiden)
- Prothrombin gene mutation PCR assay
- Protein C activity assay
- Protein S activity assay
- Antithrombin III activity assay
- Homocysteine level
- Antiphospholipid antibody assays
  - Anticardiolipin antibodies
  - Hexagonal phospholipid assay
  - Dilute Russell viper venom time

Selected Patients

- Dysfibrinogenemia evaluation
  - Fibrinogen activity level
  - Fibrinogen antigen level
  - Thrombin time
- Endogenous erythroid colony assay
- Limited evaluation for cancer

The timing of the laboratory tests is a frequent concern. The decision is whether to test during the acute event or to wait until after the patient has finished a period of anticoagulation. Heparin only interferes with the first generation coagulation assays for HRAPC and some assays for antiphospholipid antibodies. However, certain coagulation factors, especially protein C, free protein S, and antithrombin may be acutely lowered by the acute thrombosis. If the testing is performed early one can decide at that time upon duration of therapy if an abnormality is found. If the patient is to be tested later one needs to ensure the patient has been off warfarin for at least two and preferably three weeks before testing since proteins C and S are vitamin K-dependent proteins and their production will be reduced by warfarin therapy.

Although 3 - 20 percent of patients with thrombosis will have cancer diagnosed at the time of presentation, patient and clinician are often concerned about the presence of an occult underlying malignancy. This situation is similar to the patient who presents with a metastatic lesion with an unknown primary where searching for the underlying primary malignancy is often futile. Although untested, one strategy in the absence of other clinical clues is to do a limited evaluation including chest x-rays (CT in smokers), mammography, and colon cancer screening.

Testing

Factor V leiden—The most cost-effective method is to perform a coagulation-based assay for resistance to activated protein C. The newer generation assays are not affected by anticoagulation. Given that the gene mutation is constant (ARG506GLN), one can perform a DNA assay via polymerase chain reaction. The DNA assay is useful in borderline cases or in patients who are suspected to have homozygosity for the mutation.

Prothrombin gene mutation is diagnosed by the polymerase chain reaction-based test which directly detects the mutation. Although plasma levels of prothrombin are higher in these patients, just measuring the prothrombin levels cannot detect carriers of the mutation.

Protein C and protein S—Since these are vitamin K-dependent proteins, their levels will be reduced by warfarin therapy. Blood for measuring these proteins should be drawn before starting warfarin or 2-3 weeks after stopping therapy. In patients who require lifelong therapy one can perform family studies to pick up the deficiency or temporarily halt warfarin therapy for 2-3 weeks to determine the levels. Testing for "free protein S" levels should be requested since a deficiency in free protein S is more common than total protein S deficiency. Free protein S may be low (even under 30%) during a normal pregnancy. Both protein S and protein C may be low in acute thrombosis and with serious illness.

Antithrombin—Acute thromboembolism and rarely heparin therapy can lower levels. Thus, a normal antithrombin level drawn in these circumstances effectively rules this out as a cause of a hypercoagulable state. Low antithrombin levels performed in the acute setting should be repeated six weeks later (off heparin) before labeling the patient antithrombin deficient.

Therapy

The goal for warfarin anticoagulation is to keep the prothrombin time at an INR of 2.0 - 3.0. This ratio has been shown to provide the best risk-benefit ratio.

Table 17.4. Strong and weak hypercoagulable states

Strong	
	Antithrombin III deficiency
	Protein C deficiency
	Protein S deficiency
	Antiphospholipid antibody disease
	Myeloproliferative syndrome
	Cancer
	Multiple hypercoagulable states
Weak	
	Factor V leiden
	Prothrombin gene mutation
	High factor VIII levels
	Hyperhomocysteinemia

For the purposes of deciding duration of anticoagulation, both the type of hypercoagulable state and the circumstances of the thrombosis should be considered. Hypercoagulable states can be divided into "weak" or "strong" (Table 17.4). Patients with a weak hypercoagulable state who suffer a deep venous thrombosis and have a removable thrombotic risk factor should be considered for short-term anticoagulation. An example would be a woman with factor V Leiden who suffers a deep venous thrombosis while on oral contraceptives. Conversely, in the presence of a strong hypercoagulable state and thrombosis, even with a removable risk factors, one should strongly consider indefinite anticoagulation.

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CHAPTER 18

Acquired Hypercoagulable States

Acquired hypercoagulable states range from rare disorders such as Beçhet's disease to the very common initial presentation of malignancy. Acquired hypercoaguable states may present at any age. Patients with acquired disorders often present with a "flurry" of thromboses. While patients with congenital disorders may have two thromboses separated by years, the patient with an acquired hypercoagulable state may present with repeated thrombosis even on anticoagulant therapy. In some patients, thrombosis may be the first manifestation of the underlying disease. In many patients thrombosis is a well-recognized feature of the disease.

Patients suspected of having an acquire hypercoagulable state should be carefully screened for the presence of classic underlying diseases such as cancer or inflammatory bowel disease.

The most common causes of acquired hypercoagulable states—cancer, antiphospholipid antibody disease and pregnancy—are discussed in the appropriate chapters.

Inflammatory Bowel Disease

Patients with inflammatory bowel disease are at higher risk for thrombosis. Autopsy series show that 33% of patients had thrombi present. It appears that the presence of inherited hypercoagulable states also raises the risk of thrombosis in these patients. Patients with inflammatory bowel disease complicated by thrombosis usually present with deep venous thrombosis of the lower extremity. An increased risk of visceral vein thrombosis has also been reported, perhaps due to local inflammation. Rarely, large arterial thrombi have also been reported.

Pathogenesis: Patients with inflammatory bowel disease have been reported to have reduced levels of free protein S. This lower level of protein S is due to increased levels of its binding protein, C4B-binding protein, which is an acute phase reactant. Increased levels of the inflammatory cytokines such as IL-1 and TNF may also contribute to the hypercoagulable state by stimulating endothelial cells.

Diagnosis is by history. Rare patients may present with an unusual pattern of inflammatory bowel disease but most patients present with the classic signs and symptoms of bowel disease.

Therapy is with anticoagulants. One obvious difficulty is that these patient are at risk for bleeding, and severe gastrointestinal hemorrhage can complicate therapy. Fear of bleeding should not discourage adequate anticoagulation to prevent fatal thrombosis. Curiously, reports do exist showing that heparin therapy may ameliorate the inflammatory bowel disease symptoms. Therapy for the underlying bowel disease can also be helpful. Patients with ulcerative colitis experience resolution of their hypercoagulable state with total colectomy.

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

Surgery

The stress of undergoing surgery increases the risk of thrombosis in an otherwise normal patient by 10-30 fold. Recent surgery is the most common risk factor for deep venous thrombosis.

Pathogenesis of the surgical hypercoagulable state is complex. Venous stasis due to immobility during surgery and the recovery process certainly plays a role. The inflammatory response with release of inflammatory cytokines is also important. The period of relative hypercoagulability can extend for weeks after surgery. The average time to presentation with post-operative deep venous thrombosis is over two weeks after the surgery. Smoking, oral contraceptives, previous history of thrombosis, genetic hypercoagulable states, and cancer all act synergistically to increase the risk of post-operative thrombosis.

Prevention is by two methods. The first is to try to reverse any risk factors (ie, stop smoking or stop birth control pills). The other important step is to use appropriate prophylaxis for deep venous thrombosis which is discussed in detail in chapter 15.

Nephrotic Syndrome and Other Renal Disease

Nephrotic syndrome has long been associated with a hypercoagulable state. Patients with nephrotic syndrome have an increased incidence of renal vein and other thrombosis. Less well-known is that patients with renal failure in general have a higher incidence of thrombosis. Thrombosis of vascular grafts is one difficult problem. Occasional patients will suffer multiple graft thrombi which will impair their ability to undergo dialysis.

Pathogenesis of the hypercoagulable state in nephrotic syndrome is urinary loss of natural anticoagulants. Low levels of both antithrombin and protein S are commonly seen. The presence of concurrent autoimmune diseases such as lupus may add associated antiphospholipid antibodies to the mix. The hypercoagulable state seen in other renal disease is less well defined. Plasma homocysteine levels are markedly elevated in renal failure and this may play a causative role in the thrombosis.

Therapy is with anticoagulation for established thrombosis. Duration is uncertain if the underlying renal disease is eliminated. Some authorities have argued that the risk of thrombosis is so high in nephrotic syndrome that these patients should be prophylactically anticoagulated; unfortunately the associated risk of bleeding is higher in patients with renal disease due to the presence of the uremic bleeding diathesis.

Renal transplantation is also accompanied by a higher risk of thrombosis (Table 18.1). Patients with pre-existing hypercoagulable states, especially those with antiphospholipid antibodies, are at higher risk for graft thrombosis. Infusion of OKT3 has been also associated with thrombosis. Patients with a history of thrombosis should be evaluated for hypercoagulable states prior to undergoing transplantation. Patients with underlying autoimmune disease should also be evaluated for antiphospholipid antibodies. Patients should receive prophylaxis with low molecular weight heparin for the transplant and consideration should be given to avoiding routine use of OKT3 due to the associated risk of thrombosis.

No ideal solution exists for the problem of vascular graft thrombosis. One trial has suggested that antiplatelet agents may be of value in preventing occlusion.

Table 18.1. Renal transplants in hypercoagulable patients

Renal Transplant Patients at Risk for Graft Thrombosis

1. Previous AV fistula thrombosis
2. Previous venous thrombosis
3. Presence of antiphospholipid antibodies
4. Previous large vein renal transplant thrombosis

Protocol for Renal Transplant Patients at High Risk of Thrombosis

1. 2 hours before surgery, enoxaparin 20 mg subcutaneously
2. Start daily enoxaparin 20 mg subcutaneously
3. Start warfarin evening after surgery with goal INR 2-3
4. Continue warfarin for at least 6 weeks after transplant

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare hematological disorder that most often presents with low blood counts, hypocellular bone marrow and a high incidence of thrombosis. The underlying problem is a mutation in a gene which encodes a protein linking membrane proteins with the phospholipid membrane. The loss of these proteins causes a variety of clinical effects. The disease takes it name from the loss of red cell membrane proteins which inactivate complement, rendering erythrocytes more susceptible to lysis. With the advent of sophisticated testing it appears that PNH may be more common than previously believed.

Patients may present with thrombosis at any site. PNH is one of the few hypercoagulable states which classically presents with Budd-Chairi syndrome. The thrombosis associated with PNH can be refractory to oral anticoagulants and rare patients may thrombose even on therapeutic doses of heparin.

Pathogenesis of the thrombosis is unknown. There is speculation that the platelets are also more likely to be activated by complement, leading to thrombosis.

The **diagnosis** of PNH should be suspected in patients with pancytopenia and thrombosis. The classic "nocturnal hemoglobinuria" is a rare finding. Most patients will have pancytopenia although rare patients can present with elevated blood counts. Patients will usually have a high serum LDH. The older "Hams test" and sucrose hemolysis tests have been replaced by flow cytometry. Flow cytometry will directly detect membrane linking proteins. The link protein CD59 is assayed and PNH is diagnosed if more than 5% of the cells are missing this protein. This technique is very sensitive to detecting small populations of cells missing proteins.

Therapy—Patients with PNH may be very hypercoagulable. Patients who have active thrombosis should be aggressively anticoagulated. The natural history of PNH is variable. Some patients will have spontaneous regression of the disease while others will develop aplastic anemia or leukemia. Given the underlying genetic defect, this disease is a promising target for gene therapy.

Beçhet's Disease

Thrombosis is a frequent finding in patients with Beçhet's. Patients may have both arterial and venous thrombosis. Patients with Beçhet's have a predilection for both Budd-Chiari syndrome and cerebral vein thrombosis.

Pathogenesis is probably a combination of the underlying inflammatory disease and vasculitis. The arterial thrombosis is either at the site of vasculitis or due to aneurysm formation. Case reports have shown co-existing antiphospholipid antibodies in some patients with Beçhet's.

The **diagnosis** of Beçhet's disease should be considered in patients with thrombosis and any of the classic findings of Beçhet's. The major criteria for diagnosis are presence of painful mouth ulcers, iritis or posterior uveitis, and genital ulcers. Patients may have skin manifestations, gastrointestinal bleeding and central nervous system symptoms.

Therapy is with anticoagulation. Patients with severe gastrointestinal bleeding will be challenging to treat. Immunosuppression is of benefit, especially in patients with arterial disease.

Hemolytic Disorders

Patients with a broad spectrum of acquired and congenital hemolytic diseases appear to be at a higher risk of thrombosis. Higher rates of thrombosis are also seen after splenectomy for hemolytic diseases.

Pathogenesis of the thrombosis associated with hemolysis is speculated to be due to damaged red cells. One constituent of the red cell membrane, phosphotidylserine, is very effective at promoting coagulation. Usually phosphotidylserine is on the inner red cell membrane but in some congenital hemolytic anemias, phosphotidylserine is exposed due to red cell damage. This exposed phospholipid may provide a surface for coagulation reactions.

Diagnosis is by diagnosing the underlying hemolytic anemia. Higher rates of thrombosis have been seen with all hemolytic anemias and with the thalassemic syndromes.

Therapy is with anticoagulation. Some have speculated that splenectomy will worsen the hypercoagulable state. However, this potential risk of splenectomy must be balanced by any relief this operation would provide for the anemia.

Homocysteinemia

The classic genetic disease of homocysteinuria has long been associated with thrombosis. Recently it has been appreciated that even high normal or minor elevations of plasma homocysteine is associated with thrombosis. A homocysteine level over 11 mm l/L is a strong risk factor for atherosclerosis, with the risk of myocardial infarction increasing 1.5 fold for each 4 mm l/L increase in serum homocysteine. Risk of stroke and peripheral vascular disease is also increased. Elevated levels of homocysteine are also associated with a higher risk of venous thrombosis. The risk increases with levels above 18 mm l/L and increases dramatically with homocysteine levels of over 22 mm l/L.

Pathogenesis of the homocysteinemia is varied (Table 18.2) . Homocysteine is metabolized by either being converted into methionine or cysteine. The methionine conversion requires folic acid and vitamin B_{12}. The most potent risk factor is lack of dietary folic acid. Before the recent increase in folate fortification, 90% of Americans did not get 400 μg/day of folic acid and 50% did not even get 200 μg/day. In clinical nutrition studies it takes an intake of 400 μg/day to prevent an elevation of serum homocysteine. Patients with vitamin B12 deficiency will also have homocysteine elevations. Patients with increased folate requirements such as those with

Table 18.2. Influences on plasma homocysteine levels

Increased Levels	**Reduced Levels**
Genetic	Genetic
Mutations in:	Downs syndrome
cystathionine-beta-syntase	Nutritional
MTHFR	Medication
Methionine synthase	Estrogens
Nutritional	Penicillimaine
Reduced intake of:	N-aetylcysteine
folic acid	Lifestyle
cobalamin	Exercise
pyridoxine	
Diseases	
Renal disease	
Hypothyriodism	
Psoriasis	
Hemolytic anemia	
Lupus	
Medications	
Methotrexate	
Phenytoin	
Cyclosporine	
Pyrimethamine	
Trimethopirm	
Triamterene	
Lifestyle	
Cigarette smoking	
Coffee	

hemolytic anemia or psoriasis will also have elevated homocysteine. The kidney is a major organ in homocysteine metabolism, and patients with renal failure have elevated homocysteines.

Diagnosis is by measuring serum homocysteine. As with cholesterol, serum levels in the "normal" range may be associated with increased atherosclerosis. Levels below 10 mm l/L are thought desirable. In patients with premature atherosclerosis or multiple thromboses, levels above 18 mm l/L are very abnormal and are responsible, at least in part, for the thrombotic diathesis. Methionine loading can bring out latent homocysteinemia but the clinical utility is uncertain at this time. Given that homocysteine elevation is also seen with vitamin B_{12} deficiency, one should check serum methylmalonic acid (a more sensitive marker of B_{12} deficiency) if a high homocysteine level is found.

Therapy for most patients is folate replacemen (Table 18.3). The exact dose is controversial but one approach is to treat patients with a 400 μg/day supplement and remeasure the level in one month. For many patients the addition of 10-25 mg of vitamin B_6 and 1-2 mg of vitamin B_{12} to the folic acid helps to lower plasma homocysteine. The addition of vitamin B_6 may also be prudent given epidemiologic studies associating low levels of this vitamin with atherosclerosis. Some patients may require high doses of folic acid (1-5 mg po daily) to lower their homocysteine.

Table 18.3. Therapy of elevated homocysteine levels

1. Check methylmalonic acid to assess vitamin B_{12} stores
2. Start folic acid 400 μg/day along with vitamin B_6 10 mg/day and B_{12} 1mg/day.
3. Reassess levels in one month; if still elevated increase folic acid to 1 mg/day.
4. Reassess in one month. If still elevated increase folic acid to 5 mg/day.

Air Travel

Recently much attention has been given to thrombosis due to airplane travel. Case-control studies suggest a relative risk of thrombosis of 3-4 fold with prolonged (over four hours) travel with a high risk for longer travel times. It is uncertain what the absolute risk for thrombosis is. The overall risk of symptomatic pulmonary embolism is estimated to be 0.4 per million passengers rising to 4 per million in the highest risk group. In contrast, a small prospective trial showed a calf vein thrombosis rate of up to 12%. The presence of risk factors such as history of deep venous thrombosis is important. Up to 70-90% of those with thrombosis had other risk factors for thrombosis.

Pathogenesis is controversial. Venous stasis appears to be the primary risk factor. The hypoxia is uncertain given that most studies do not show activation of coagulation with mild hypoxic exposure. Pre-existing risk factors for thrombosis are also important. As noted above most studies indicated that the people who develop travel related thrombosis have other risk factors such as history of thrombosis, estrogen use, etc...

Therapy—The best method of prophylaxis is controversial. Elastic stockings provided protection in one trial. Another trial has shown benefit for heparin (but not aspirin!) but this is inconvenient for most people. A reasonable approach may be to recommend stockings and encourage foot movement for most people. It may be sensible to offer patients with history of thrombosis or hypercoagulable states LMWH prophylaxis before very long (> 6hour) flight.

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CHAPTER 19

Antiphospholipid Antibody Syndrome

Antiphospholipid Antibodies (APLA)

APLA are antibodies directed against certain phospholipids. They are found in a variety of clinical situations. APLA are important to detect because in certain patients they are associated with a syndrome which includes a hypercoagulable state, thrombocytopenia, fetal loss, dementia, strokes, optic changes, Addison's disease, and skin rashes.

The underlying mechanism leading to the clinical syndrome associated with APLA is still unknown. Perhaps the antibodies inhibit the function of proteins C or S, damage the endothelium, activate platelets or inhibit prostacyclin. Despite several decades of research, the etiology of the thrombotic tendency associated with APLA remains unknown.

Semantics

APLA syndrome—Patients with APLA and one "major clinical criterion" are said to have "APLA syndrome." The major clinical criteria include venous or arterial thrombosis (including neurological disease such as stroke), thrombocytopenia, or frequent miscarriages. (Table 19.1)

Secondary APLA syndrome is APLA plus another autoimmune disease, most commonly lupus.

Primary APLA syndrome is APLA syndrome occurring outside of the setting of lupus. In distinction to SLE-APLA patients, primary APLA patients are more often male and will have low titer ANA's but no other criteria for SLE.

Anticardiolipin antibody is an APLA in which the antibody is detected by an ELISA assay.

Anti-beta$_2$glycoprotein (Anti-β_2GP) is a subgroup of APLA also detected by ELISA assay. Anti-β_2GP are thought to be more specific for APLA that cause thrombosis.

Table 19.1. Diagnosis of antiphospholipid antibody syndrome

Positive antiphospholipid antibody test or lupus inhibitor test that is persistent when tested at least 6 weeks apart with at least one clinical feature:

- Arterial or venous thrombosis
- Thrombocytopenia
- Frequent miscarriages
  - 3 or more first trimester losses
  - 2 or more second trimester losses
  - 1 or more third trimester loss

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"Lupus anticoagulant" and "lupus inhibitor" are terms which are interchangeable. Lupus inhibitor is an APLA in which the antibody is detected by a coagulation test.

Who Gets APLA?

Approximately 30-50% of patients with SLE will have APLA. The antibodies can also be found in patients with other autoimmune diseases. Patients without lupus or other autoimmune disease can have symptomatic APLA ("Primary APLA Syndrome"). Children will often develop transient non-thrombotic APLA after viral infections. This laboratory finding often comes to attention during pre-operative evaluation for tonsillectomy. Up to 30% of patients with HIV infection will also develop APLA. The infection-associated APLA are not associated with thrombosis and are usually Anti-β_2GP negative. Medication may also induce APLA. Chlorpromazine is the most common cause, but APLA has also been associated with use of procainamide, dilantin and quinidine. In screening studies of blood donors and normal controls, up to 10-20% of asymptomatic people have APLA. However, the APLA in these people are usually low-titer and most often occurs in young women.

APLA: Clinical Associations

APLA are associated with a number of disease states (Table 19.2). The best described conditions are venous thrombosis, arterial thrombosis, neurological disease, frequent miscarriages, and thrombocytopenia.

Venous thrombosis. Venous thrombosis was the first described manifestation of APLA and is the one most clinically predominant. Overall, retrospective studies show that 31% of patient with APLA have venous thrombosis. Patients with lupus and APLA have a thrombosis rate of 42%; patients with infectious or drug-induced APLA have a thrombosis rate of less than five percent. Patients with APLA are over-represented in young patients with deep vein thrombosis. Prospective studies have demonstrated a relative risk for venous thrombosis of 5.3 for patients with IgG anticardiolipin antibodies. Patients with APLA-associated venous thrombosis may be difficult to treat. These patients have high rates of recurrent thrombosis (20-50%/year) if anticoagulation is stopped. Occasional patients may be refractory to warfarin and will need to be on long-term heparin therapy.

Arterial disease. The incidence of APLA is increased in young patients with myocardial infarction and especially stroke. APLA are also found in a higher proportion in patients with peripheral vascular disease and may be predictive graft failure. Prospective studies have demonstrated that patients with APLA have higher rates of saphenous bypass vein occlusion and re-occlusion of PTCA.

Neurological disease. A variety of neurological disorders have been associated with APLA. The underlying cause of these disorders appears to be thrombosis. Some patients have large vessel disease while more often patients have small vessel involvement. Patients with APLA often will have multiple MRI abnormalities consistent with small white matter infarcts. The neurological diseases include:

Stroke. APLA is found in 10-46% of young patients with stroke and in 10% of stroke patients overall. Stroke patients with APLA tend to be younger (42 years vs 62 years). These patients also have a recurrence rate of 6-30%/year and a mortality rate of 10%/year. Certain groups of patients appear to be at even higher risk of recurrence. These would include SLE patients with APLA and patients with Sneddon's syndrome (described below).

Table 19.2. Clinical syndromes

Venous thrombosis
Lower extremity
Cerebral vein thrombosis
Neurologic disease
Strokes
Dementia
Pregnancy complications
Second trimester miscarriages
HELLP syndrome
Thrombocytopenia
Adrenal insufficiency
Hypoprothrombinemia
Cardiac valve damage
Skin disease
Livedo reticularis
Livedo vasculitis
Superficial thrombophlebitis

Early-onset dementia. This is becoming a well-recognized and feared feature of APLA. The dementia is multi-infarct in nature and occurs often without a history of major stroke episodes. APLA-related dementia on the average occurs a decade earlier (52 years) than non-APLA dementia. Sneddon's syndrome is a combination of livedo reticularis and cerebral ischemic events. Sneddon's is a form of APLA which often results in major morbidity and mortality. The skin involvement in Sneddon's may be severe enough to result in ulceration. Patients with Sneddon's syndrome seem also to have a high incidence of thrombocytopenia.

Ocular events. Amaurosis fugax, retinal artery thrombosis, and retinal vein thrombosis have been reported as part of APLA syndrome in multiple case reports.

Other. APLA are found in as many as 50% of patients who get migraines. As will be discussed below, patients may have encephalopathy as part of severe APLA.

Fetal loss. Fetal loss is seen in 38% of SLE patients with APLA. The incidence of fetal loss in non-SLE APLA is controversial. When women who have recurrent fetal loss are screened the incidence of APLA is 30%. The pathophysiology is thought to be due to placental microthrombosis. The incidence of HELLP syndrome is higher in these patients and tends to occur earlier in the pregnancy. Fetal growth retardation is also common due to placental infarctions.

Thrombocytopenia. Certain APLA will react with activated platelets, leading to thrombocytopenia. Only activated platelets expose the proper phospholipid epitopes that the APLA react with. Therefore, it is the patients with the thrombotic manifestations of APLA who will also get the thrombocytopenia. The treatment of these patients is clinically challenging since the thrombocytopenia often occurs in patients who are anticoagulated for thrombosis. Danazol appears to be uniquely effective for these patients.

Hypoprothrombinemia. Patients with APLA (almost always those with lupus inhibitors) may have an elevated prothrombin time (PT) for two reasons. The APLA may be present in such high titers that they will also interfere with the PT test. Alternatively, 10% of patients with lupus inhibitors will develop non-neutralizing antibodies to prothrombin. This leads to increased clearance of prothrombin from

Table 19.3. Catastrophic antiphospholipid antibody syndrome (CAPS)

- Cardiac disease: cardiomyopathy
- Pulmonary disease: pulmonary hemorrhage, ARDS
- Neurologic disease: seizures, coma, encephalopathy
- Renal disease: renal failure due to thrombosis
- Skin disease: livido reticularis, skin necrosis
- Bone: necrosis
- Severe thrombocytopenia

the plasma and hypoprothrombinemia. Since patients with hypoprothrombinemia can present with hemorrhagic complications, it is important to check for this when faced with an APLA patient with an elevated PT-INR. The work-up includes a 50:50 mix on the PT and a measure of the plasma level of prothrombin. Plasma infusions and steroids are effective in raising the prothrombin level in patients with prothrombin antibodies.

Other associated diseases. Patients with APLA may have an assortment of skin findings included livedo, Raynaud's phenomenon, ulcers, and superficial thrombophlebitis. Up to 26% of patients with SLE and APLA have cardiac valve vegetations and mitral regurgitation. Rarely patients have had valve destruction so extensive as to require valve replacement. Myocardial dysfunction is seen in 5% of SLE-APLA patients. Primary pulmonary hypertension has been associated with APLA. Ten percent of patients with chronic thromboembolic pulmonary hypertension have APLA. Adrenal insufficiency from microvascular thrombosis has also been seen in APLA patients.

Catastrophic APLA (CAPS)

Rarely, patients with antiphospholipid antibody syndrome can present with fulminant multiorgan system failure. CAPS is caused by widespread microthrombi in multiple vascular fields. These patients will develop renal failure, encephalopathy, adult respiratory distress syndrome (often with pulmonary hemorrhage), heart failure, dramatic livedo reticularis, and worsening thrombocytopenia (Table 19.3). Many of these patients have pre-existing autoimmune disorders and high titers of anticardiolipin antibodies.

It appears that the best therapy for these patients is aggressive immunosuppression with plasmapheresis then (perhaps) IV cyclophosphamide monthly. Early recognition of this syndrome can lead to rapid therapy and resolution of the multiorgan system failure.

Diagnostic Approach

As reviewed extensively in chapter two, there is unfortunately no one screening test for APLA (Table 19.4) One must perform the entire diagnostic panel on patients suspected of having APLA. A good screen is to perform: 1) Anticardiolipin antibodies, 2) dRVVT 3) "Lupus Inhibitor Screen" (different aPTT reagents). One caveat in testing is that levels of APLA may fall during thrombotic events. Patients with an isolated thrombosis and only low titers of APLA should have the APLA retested in six weeks to ensure these were not transient APLA related to infection.

Patients with persistent lupus inhibitors and thrombosis are at very high risk of recurrent events. In general, APLA are significant if they are of medium or high titer

Table 19.4. APLA diagnosis

Anticardiolipin Antibodies
or
Demonstration of Lupus Inhibitor
Principles of demonstrating lupus inhibitor:
1. Prolongation of coagulation based test
2. Failure of correction in 50:50 mix
3. Correction of abnormal test with addition of phospholipid
Coagulation-Based Tests for Lupus Inhibitor
Dilute Russell viper venom time
Hexagonal phospholipid assay

and persistence. Given the prevalence of low-titer APLA the significance of these is unknown. One approach is to test for the presence of anti-$\beta_2$glycoprotein (anti-$\beta_2$gp) in these patients if they have persistently positive low-titer APLA. Patients who are anti-β_2GP positive should be considered to have APLA.

Occasional patients are seen who consistently have negative laboratory testing for APLA but have many of the clinical features of APLA such as thrombocytopenia, thrombosis and miscarriages. It is probable that these patients do have "APLA-negative APLA syndrome" and they should be treated as such.

Therapy

Although there are few prospective trials of therapy in APLA, several lessons may be learned from retrospective studies (Table 19.5) While APLA does appear to be an autoimmune disease, immunosuppression does not prevent recurrent thrombosis, fetal loss, or neurological syndromes. Therefore, immunosuppression should not play a role in the therapy of thrombotic APLA. The only exception to this is "catastrophic APLA" where plasmapheresis plays a crucial role.

It used to be thought that anticoagulation with warfarin to an INR of 3.0-3.5 appears to be effective in patients with APLA. However, a recent randomized trial demonstrated that an INR range of 2.0-3.0 was just as effective as the higher INR range. As mentioned above, some patients will fail warfarin and will required more

Table 19.5. APLA therapy

Venous or arterial thrombosis: warfarin with target INR 2.0-3.0
Warfarin-refractory cases: enoxaparin 1 mg/kg every 12 hours
Pregnancy:
History of thrombosis: enoxaparin 1 mg/kg every 12 hours
No thrombosis: enoxaparin 40 mg/day ± aspirin
Complications:
Thrombocytopenia:
Short term: prednisone 60 mg/day ± immunoglobulin or anti-D
Long term: danazol 200 mg po qid
Hypoprothrombinemia: prednisone 60 mg/day
Catastrophic APLA syndrome:
Plasma exchange
Cyclophosphamide 1 gram/meter squared IV every 28 days

aggressive anticoagulation. There was initial enthusiasm for aspirin and prednisone to prevent miscarriages in pregnant women with APLA. It now appears that heparin anticoagulation is more effective.

Thrombocytopenia. Thrombocytopenia in patients with APLA occurs in those patients prone to thrombosis. The low platelet counts makes anticoagulation hazardous. In addition, patients with APLA are often high surgical risks. Thrombocytopenia may respond to steroids, immunoglobulin and IV-anti-D. Danazol 200 mg po QID is effective in many patients with APLA-related thrombocytopenia. One should ensure an adequate (6 months) therapeutic trial is given.

Pregnancy and APLA. This is the most controversial area of treatment. One approach is based on previous history. If there is a history of thrombosis, LMW heparin in therapeutic doses is used throughout the pregnancy. For frequent miscarriages, prophylactic doses of LMWH are used along with 81 mg of aspirin. Limited data suggests that prior to conception the use of 81 mg of aspirin daily may be effective in aiding conception.

Difficulties in Monitoring Anticoagulation

Since APLA react with phospholipids, both the aPTT and the protime can be affected. If standard heparin is used to anticoagulate patients with APLA, treatment must be followed by monitoring heparin levels (target range 0.35 - 0.70 anti-Xa units 6 hours after the injection). The predictable dosing and anticoagulant effect is one advantage of using LMW heparin acutely for thrombosis in APLA patients. One should measure LMW heparin levels in patients with APLA on long-term therapy (0.7 - 1.1 anti-Xa units four hours after injection) or in those patients with renal failure.

Often patients with APLA will have minor elevations of PT-INR. Those few patients with elevated protimes due to a lupus inhibitor can be very difficult to manage with warfarin. One option is to perform prothrombin and proconvertin times ("P&P") to follow anticoagulation. The P&P is less dependent on phospholipids and is not affected by the APLA. The therapeutic range is 15 - 30%. A lower percentage means greater anticoagulation. Another option is to measure levels of factor X. A chromogenic assay (not affected by APLA) is available. The therapeutic range of 0.15 - 0.30 factor X units has been shown to best correlate with therapeutic warfarin effect. The other option is to use long-term heparin.

One difficult issue is that of the patient with APLA with no thrombotic manifestations. Although some of these patients are at risk, especially those with SLE, many will never develop thrombosis. The current recommendation would be to search thoroughly for thrombosis. The work-up would include a brain MRI in patients with SLE or in patients with any neurological symptoms. If this work-up is negative for prior thrombosis, then the patient is followed very closely.

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CHAPTER 20

Antithrombotic Therapy for Cardiac Disease

Antithrombotic therapy is used for two major purposes in the treatment of cardiac disease. The first is the prevention of embolic disease and the other is for treatment of ischemic heart disease (Table 20.1). Detailed antithrombotic management of percutaneous coronary interventions (PCI) is described in the antiplatelet chapter.

Ischemic Heart Disease

The underlying pathogenesis of ischemic heart disease is the gradual development of an atherosclerotic plaque. Patients develop clinical symptoms either through diminution of blood flow through a stenotic vessel or with acute ischemia due to thrombus formation on a ruptured plaque. The realization that acute thrombus formation underlies most acute presentations of ischemic heart disease has revolutionized cardiology.

Primary Prevention

Four of five clinical trials using aspirin have established that it is effective in primary prevention of myocardial infarction. The side effects of gastrointestinal bleeding and, more importantly, intracranial hemorrhage, occur more frequently with aspirin use. In the lowest risk patients the use of aspirin is not warranted. Patients with even modest risk factors should be on aspirin therapy unless there is a contraindication. Most men and women over 50 years of age are aspirin candidates. Patients under 50 years of age with evidence of atherosclerotic vascular disease or with any risk factors should also be considered for aspirin therapy.

Stable Angina

Patients with stable angina or with clinical evidence of coronary artery disease should receive aspirin 75-325 mg/day indefinitely. Clopidogrel 75 mg/day can be substituted in aspirin-intolerant patients.

Unstable Angina

All patients with unstable angina should chew aspirin 160-325 mg as soon as possible, and a dose of 75-325 mg daily should be continued indefinitely. Recent data suggest an additional benefit by adding clopidogrel 75 mg/day to aspirin. In addition, those with persistent pain, EKG changes, or non-Q wave myocardial infarctions should receive therapy with enoxaparin 1mg/kg q12 hours along with the aspirin until their pain resolves. Enoxaparin has been shown to be superior to standard heparin in two trials.

The GP IIb/IIIa inhibitors have also been shown to be useful in unstable angina syndromes. Both tirofiban, a synthetic non-peptide antagonist, and eptifibatide, a

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Table 20.1. Therapy of ischemic heart syndromes

Primary Prevention
Aspirin 75-325 mg/day
Stable Angina
Aspirin 75-325 mg/day or clopidogrel 75 mg/day
Unstable Angina
Aspirin 160-325 mg initially then 75-160 mg/day
Persistent pain, EKG changes or non-Q wave MI:
Aspirin 160 -325 mg plus
Enoxaparin 1 mg/kg every 12 hours plus either:
Tirofiban 0.4 μg/kg/min bolus 30 minutes and then an infusion of 0/1 μg/kg/min
or
Eptifibatide 180 μg/kg bolus followed by 2 μg/kg/min for up to 72 hours.
Acute Myocardial Infarction
Aspirin 160-325 initially then 75-160 mg/day
Thrombolytic therapy:
Streptokinase—1.5 million units IV over one hour.
Anistreplase —30 units IV over 5 minutes.
TPA—15 mg/kg bolus, 0.75 mg/kg over 30 minutes, then 0.5 mg/kg over next hour.
Reteplase two 10 units bolus separated by 30 minutes.
Tenecteplase is weight-based bolus over 5 seconds.
<60 kg = 30mg
60-69 kg = 35mg
70-79 kg = 40mg
80-89 kg = 45mg
>90 kg = 50mg
Adjunctive therapy to thrombolytic therapy:
tPA, reteplase, tenecteplase—Heparin 75 units/kg bolus with start of tPA and 1000 units/hr maintenance, adjusted to keep aPTT 1.5-2.0 times control *or* enoxaparin 30 mg IV and then 1 mg/kg every12 hours.
SK and APSAC—Heparin 1000 units/hr maintenance, adjusted to keep aPTT 1.5-2.0 times control starting 1-3 hours after SK

peptide antagonist, reduced myocardial infarctions and deaths when used with heparin and aspirin in unstable angina patients. Abciximab has also been used for this indication but is only effective if percutaneous coronary intervention (PCI) is planned. Surprisingly, abciximab when used without PCI for unstable angina appears to be inferior to heparin and aspirin.

Currently, management of the high-risk patient (ST changes, positive troponins, previous infarct) with unstable angina consists of combined modality therapy of aspirin, clopidogrel, enoxaparin, and if available, PCI with stent placement.

Acute Myocardial Infarction: Acute Therapy

The patient who presents with chest pain needs to be rapidly evaluated for myocardial ischemia. Patients with evolving myocardial infarctions require rapid therapy to re-open the occluded coronary artery. Currently patients may be either treated with thrombolytic therapy or may undergo immediate coronary angioplasty. Data does suggest that if PCI can be performed within 3-6 hours, it is preferable to thrombolytic therapy. All patients with AMI, no matter what the definitive therapy will be, should chew and swallow a nonenteric-coated aspirin (160-325 mg) as soon as possible.

Thrombolytic Therapy

Thrombolytic therapy reduces in-hospital mortality and increases one-year survival in patients suffering from AMI. Currently there is increasing interest in immediate PCI for patients with acute MI based on trials suggesting improved outcomes. Therefore thrombolysis or PCI should be considered in *every* patient with evolving AMI.

Trials showing benefits of thrombolytic therapy used these criteria to predict evolving AMI: at least one-half hour of ischemic chest pain and either at least 1 mm ST elevation in two adjacent limb leads or 1-2 mm ST elevation in two adjacent precordial leads. Patients with pain and complete bundle branch block also showed benefit from thrombolytic therapy. Patients with pain and ST depression or a normal ECG do *not* benefit from thrombolysis. Thrombolytic therapy should be started as soon as possible up to 6 hours from onset of AMI. Thrombolytic therapy may be beneficial 6-24 hours after therapy in selected patients (i.e., ongoing pain without full evolution of Q waves). Patients with anterior MIs, those over 70 years of age, and those with previous MI have a higher mortality with AMI and should be strongly considered for thrombolytic therapy (if immediate PCI is not available).

Choice of Drug and Dosing

Results of early head-to-head comparisons of thrombolytic agents (TIMI, ISIS-3, GISSI-2) showed that the three current agents available- streptokinase (SK), APSAC (anisoylated-plasminogen-SK complex) and tissue plasminogen activator (tPA), were essentially equivalent. TPA superiority in 90 minute reperfusion rates was outweighed by high rates of rethrombosis and adverse cerebral events. However, the GUSTO trial has shown that tPA combined with continuous heparin is slightly superior to SK. The results of the GUSTO trials were significant due to the large number of patients and it is not clear whether the apparent superiority of tPA is seen in all patient groups or is even real. Therefore, the final choice of agents remains a source of some contention. Given the ease of use of "second generation" tPA agents, these are becoming the most popular thrombolytic agents. The only clear indication for tPA or second generation agents is in those who have recently received SK or who have had a recent strep infection. It is more important to ensure that the selected patient will receive some sort of timely reperfusion therapy rather than be overly concerned about which agent should be given. Accumulating data shows that early PCI may be as good or better than thrombolysis and should be strongly considered in patients with any contraindication to thrombolysis.

The agents and recommended dosages:

SK—1.5 million units IV over one hour.

APSAC—30 units IV over 5 minutes.

tPA—15 mg/kg bolus, 0.75 mg/kg over 30 minutes, then 0.5 mg/kg over next hour.

Reteplase two 10 unit boluses 30 minutes apart.

Tenecteplase is weight-based (see Table 20.1) and given as a bolus over 5 seconds.

Adjuvant Therapy to Thrombolytic Therapy

All patients should receive 160-325 mg of aspirin ASAP. Given the results of GUSTO, heparin should be given with weight-based bolus of 60 units/kg followed by a 12 units/kg/hr infusion to maintain an aPTT equivalent to an anti-Xa level of

to 0.14 to 0.34 in patients receiving tPA, reteplase, and tenecteplase. The use of heparin with other thrombolytic agents is less well-established and is not recommended for SK unless other indications are present for full anticoagulation. Suggested heparin dosing:

tPA, reteplase, tenecteplase—Weight-based bolus of 60 units/kg followed by a 12 units/kg/hr infusion to maintain an aPTT equivalent to an anti-Xa level of to 0.14 to 0.35, or enoxaparin 30 mg IV bolus and then 1 mg/kg every 12 hours.

SK and APSAC—Heparin 1000 U/hr maintenance, adjusted to keep aPTT 1.5-2.0 times control starting 1-3 hours after SK.

As with other AMI patients, post-lytic therapy patients should receive aspirin, statins, and beta-blockers. Patients should receive warfarin if they fall into one of the high-risk categories listed under AMI. Evidence is accumulating that post-MI warfarin may be more effective than aspirin in preventing recurrent MI but the cost and need for monitoring of warfarin remains problematic.

Acute Myocardial Infarction (AMI): Long-Term Antithrombotic Therapy

Patients suffering from AMI are at risk for a variety of thrombotic complications ranging from re-infarction to stroke. Therefore, all patients suffering from AMI should be considered for anticoagulation (Table 20.2).

The following groups of patients should receive therapeutic heparin or LMW heparin followed by warfarin (INR 2.0-3.0) for 1-3 months:

1. Severe LV dysfunction.
2. Congestive heart failure.
3. History of systemic or pulmonary embolism.
4. Mural thrombus on echocardiography.
5. Atrial fibrillation (indefinite warfarin therapy).
6. Anterior Q-wave infarction.

Other patients should receive heparin 7,500 units BID or prophylactic dose LMW heparin daily for either 7 days or until fully ambulatory.

Aspirin should be continued at 160-325 mg indefinitely even if heparin is given. However, if warfarin is given as outlined above, the aspirin should be held until after the course of warfarin. Patients with contraindications to post-AMI aspirin should be treated with warfarin to an INR of 3-4.5.

CABG

Aspirin 325 mg/day, started 6 hours after surgery, reduces the rate of graft closure and is recommended.

Table 20.2. Acute myocardial infarction: Indications for warfarin anticoagulation therapy

- Severe LV dysfunction.
- Congestive heart failure.
- History of systemic or pulmonary embolism.
- Mural thrombus on echocardiography.
- Atrial fibrillation (indefinite warfarin therapy).
- Anterior Q-wave infarction.

PCI

Therapeutic heparin is recommended for at least 2-4 hours after simple procedures and for up to 24 hours in complicated patients. Aspirin 325 mg should be given before the procedure and should be continued indefinitely at a dose of 75 mg - 325 mg/day. Abciximab therapy has been shown to be beneficial in all groups of patients undergoing angioplasty and its use should be strongly considered in any high-risk patient. Abciximab is administered in a dose of 0.25 μg/kg plus 0.125 μg/kg/min (maximum 10 mg/min) for twelve hours. The risk of bleeding with abciximab was greatly reduced when less heparin was used with no loss of effectiveness. Currently, when using abciximab, the recommended heparin dose is 70 units/kg (maximum 7000 units) bolus with additional bolus to achieve an activated clotting time (ACT) of 200 seconds. Excess bleeding was also prevented by early sheath removal when ACT <175 sec.

Evaluation of the Young Patient with Acute Myocardial Infarction

Myocardial infarction in men under age 40 and women under age 50 is unusual. Myocardial infarction at these young ages can be due to reasons other than atherosclerosis. The most common other reasons are embolic occlusion, congenital defects in the coronary arteries, and vasculitis.

Unless the etiology is obvious, young patients with acute myocardial infarction should undergo coronary angiography to determine their coronary anatomy. Embolic occlusion of coronary arteries is common in patients with endocarditis and in under-anticoagulated patients with mechanical heart valves.

Patients with premature myocardial infarctions should receive a limited evaluation for hypercoagulable states. There is no convincing evidence that deficiency of protein S, protein C, antithrombin or the presence of the factor V Leiden mutation increases risk of MI or stroke. Patients should be evaluated for the presence of antiphospholipid antibodies, undergo a full lipid profile and have a homocysteine level determined. Given the association with premature atherosclerosis, levels of lipoprotein(a) should also be determined.

Therapy is uncertain. Patients with an embolic source (unless due to endocarditis) should probably receive full anticoagulation with warfarin. Patients with premature atherosclerosis should undergo aggressive antilipid therapy and should be placed on aspirin.

Prevention of Embolism

Atrial Fibrillation

Atrial fibrillation is the most common cardiac condition leading to embolism. The risk of stroke due to embolism in patients with atrial fibrillation is 3-7%/year. As will be discussed below, several groups of patients have been identified as being at higher risk for embolism.

Recently eight well-designed studies have clarified the role of anticoagulant therapy. These studies examined stroke prevention in patients with nonvalvular atrial fibrillation. The warfarin trials have established the role of warfarin anticoagulation in reducing the risk of stroke from 5%/year down to 1%/year with low rates of hemorrhage.

Table 20.3. Risk factors for stroke in patients with atrial fibrillation

Clinical Risk Factors
Hypertension
Recent congestive heart failure
History of embolism
Echocardiographic Risk Factors
Global LV dysfunction
Left atrial diameter> 2.5 cm/m^2

Table 20.4. Risk of stroke/year in patients with atrial fibrillation

Clinical Factors	**Strokes/Year**
No risk factors	2.5%
1 risk factor	7.2%
> 2 risk factors	17.6%
Clinical Plus Echo	**Strokes/Year**
No risk factors	1.0%
1-2 risk factors	6.0%
> 3 risk factors	18.6%

It is clear from reviewing these studies that warfarin is indicated for prevention of embolism in many at-risk patients with nonvalvular atrial fibrillation. The practicing clinician needs to consider several factors prior to initiating warfarin therapy for everyone with atrial fibrillation. One is that the patients in these trials were selected specifically and did not have risk factors for bleeding. These patients also had their anticoagulation aggressively managed. Several studies have shown that patients followed in anticoagulation clinics have a lower risk of bleeding than those followed by their physician. Finally, these patients chose to be in a study and were more likely to be compliant than the average patient.

The issue of aspirin use remains unresolved. The AFASAK trial showed aspirin to be of no benefit in the prevention of embolism. SPAF showed ASA was effective but only in patients under 74 years of age. SPAF III demonstrated that in low-risk patients, aspirin was effective in preventing embolism. Low-risk patients were defined as those without a history of embolism, hypertension, or recent heart failure, and who were not women over the age of 75. Aspirin is a prudent choice for patients without these risk factors.

Data now exists to risk-stratify patients and help the clinician choose between warfarin and aspirin. As shown in Tables 20.3 and 20.4, the SPAF study found 3 clinical and 2 echocardiographic findings which can segregate patients into high- and low-risk groups. Patients with a stroke risk of 1-2% (under age 75) should be considered for aspirin therapy and the high-risk patients (risk greater than 10%) should receive warfarin. Patients without risk factors for bleeding and with one risk factor for embolism should be considered for warfarin therapy. Their risk of stroke is higher than the risk of serious hemorrhagic complications of warfarin. A subgroup analysis from SPAF suggests that warfarin protects against embolic stroke while aspirin protects against non-embolic stroke in patients with atrial fibrillation. In low-risk

patients atrial fibrillation may a marker for cerebrovascular disease for which aspirin might offer protection.

When available, Ximelagatran will be an useful alternative to warfarin in many patients with atrial fibrillation. Two clinical trials comparing this agent to warfarin have shown that ximelagatran is just as effective in stroke prevention with no increased risk of bleeding. Ximelagatran offers the advantage of predicable dosing because of food or drug interactions. The dose is 36 mg. Since 3-6% of patients when starting this drug sill have liver function test abnormalities, these should be monitored. In addition, ximelagatran is renal cleared and there is no data yet on renal dosing.

Atrial Fibrillation—Special Situations

Patients with atrial fibrillation undergoing *cardioversion* are at risk for embolism with up to a 5% incidence. Consequently patients with atrial fibrillation of greater than two days duration should receive warfarin to achieve an INR of 2.0-3.0 for a duration of three weeks prior to cardioversion. This should allow any thrombus present to organize. Since mechanical activity of the atria may not fully resume until some time after resumption of normal sinus rhythm, patients should remain anticoagulated for 4 weeks after cardioversion. The same procedure should be followed for patients undergoing chemical cardioversion for atrial fibrillation.

Atrial fibrillation in *thyrotoxic heart disease* is associated with a high rate of embolic phenomena. Therefore, these patients should receive warfarin to maintain an INR of 2.0-3.0 until 4 weeks after the resumption of normal sinus rhythm.

Rheumatic Valve Disease

Patients with rheumatic mitral valve disease are at a risk for stroke which may be as high as 20% per year. Thus, patients with rheumatic mitral valve disease should receive warfarin (INR 2.0-3.0) if they have one of the following:

1. History of embolism
2. Chronic or paroxysmal atrial fibrillation
3. Normal sinus rhythm and left atrial diameter >5.5 cm.

Patients with recurrent emboli despite warfarin should receive 80-100 mg/day of aspirin in addition to their warfarin.

Mechanical Prosthetic Heart Valves

Patients with mechanical heart valves are at extremely high risk for embolization and anticoagulation is strongly recommended (Table 20.5). Currently much debate exists about the best anticoagulation protocol for valve patients. Certain patients and valves are at higher risk of embolic events than others. Patients with tilting valves in the aortic position have a lower risk of emboli, and patients with a caged ball or multiple valves are at higher risk. One approach is to risk-stratify patients as follows:

- Bi-leaflet valve in aortic position: INR 2-3
- Caged ball valve: INR 2.5-3.5 with 80-100 mg/day aspirin
- Others: INR 2.5-3.5, or INR 2-3 with 80-100 mg/day aspirin
- Patients with risk factors such as atrial fibrillation, previous embolism or coronary artery disease should be considered for combined therapy.

One frequent concern is the patient with a valve who needs a procedure or is bleeding. It should be remembered that although the risk of emboli or stroke is high over the long run, the risk of emboli or valve thrombosis is low when considered day by day. Risk of valve emboli or thrombosis for a valve in the aortic position is shown

Table 20.5. Risk stratification and therapy of mechanical valve patients

High Risk
Treat to INR 2.5 - 3.5 + ASA 80-100mg/day.
Valve implanted before 1980
Previous embolism
Vascular disease
Risk of stroke >2%/yr on warfarin alone
Medium Risk
INR 2.5 - 3.5
Low Risk
INR 2-3
Bileaflet valve in aortic position
Treatment and Risk Stratification of Bioprosthetic Valves
AVR or MVR: INR 2.5 - 3.5 for 3 months then ASA
+ a fib: INR 2-3
+ hx embolism, vascular disease or LA thrombus:
INR 2.5-3.5 + ASA 80 - 100 mg/day

Table 20.6. Risk(%) for embolic events when off anticoagulation (Pauker, JAMA)

Aortic Position	One Day	Two Weeks	One Year
Ball	0.03	0.44	11
Bjork	0.03	0.38	10
St Jude	0.02	0.21	5
Mitral Position			
Ball	0.08	1.13	30
Bjork	0.05	0.74	19
St Jude	0.03	0.48	13

in Table 20.6. It is relatively safe for short periods of time to stop anticoagulation. One should avoid large doses of vitamin K (greater than 1-2 mg) for reversal of warfarin anticoagulation. The higher doses of vitamin K are no more effective than lower doses, and when the patient needs to be restarted on warfarin it will take a much longer time to reach a therapeutic prothrombin time when high doses of vitamin K have been used.

Bioprosthetic Heart Valves

Although the risk is lower, bioprosthetic hearts valves still have a definite risk of associated embolization. This is highest immediately after surgery and in patients with bioprosthetic valves who have other risk factors such as atrial fibrillation. Therefore patients with a new bioprosthetic valve should be anticoagulated for 3 months after surgery with warfarin to an INR of 2.0-3.0. Furthermore, patients with atrial fibrillation, history of embolism or those with left atrial thrombi should be anticoagulated indefinitely with warfarin.

Chronic Heart Failure

Patients with left ventricular ejection fractions under 30% associated with global dysfunction have rates of stroke of 3-4%/year. In addition, these patients are also at risk for venous thrombosis with as many as 20% of these patients dying of venous

thrombotic disease. Unfortunately this group of patients has not been well-studied, but patients with global cardiac dysfunction should be considered candidates for anticoagulation, especially if they have had previous emboli.

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CHAPTER 21

Stroke and Peripheral Vascular Disease

Stroke

Cerebrovascular disease may be caused by atherosclerosis, embolism, or unusual causes such as vasculitis. Most strokes are due to either atherosclerosis or embolism and discussion here will focus on these causes. However, the clinician must be alert to more unusual causes of stroke in selected cases.

Acute Stroke

The patient with acute neurological defects demands a rapid decision as to whether the defect is ischemic in nature and, if so, what therapy should be instituted (Table 21.1). Patients with symptoms less than three hours old are candidates for thrombolytic therapy. Evaluation of these patients should be rapid. Patients should undergo a CT scan to rule out hemorrhage or mass lesion. Evaluation for an underlying systemic process should also be undertaken.

Patients who meet rigorous NINDS trial criteria should be considered for thrombolytic therapy (Table 21.2). Thrombolytic therapy is believed to be associated with an improvement in clinical outcome but the rate of intracranial hemorrhage is high and patient selection is crucial. The rate of bleeding complications is increased in patients who did not meet the NINDS criteria but still received thrombolytic therapy. Absolute contraindications to thrombolytic therapy include CT evidence of intracranial hemorrhage, systolic blood pressure greater than 185 mmHg or diastolic greater than 110 mm Hg, or a seizure with or before stroke onset. Patients who undergo thrombolytic therapy should receive tPA 0.9 mg/kg (maximum 90 mg) with ten percent of the dose given in one minute. The rest should be given over one hour. Patients who receive thrombolytic therapy should not receive any other form of anticoagulation including aspirin for 24 hours. These patients should be carefully monitored for signs of bleeding.

Table 21.1. Antithrombotic therapy of cerebrovascular disease

Transient Ischemic Attack	
	Ipsilateral carotid stenosis > 69%: endarterectomy
	Others: aspirin 75-160 mg/day or clopidogrel in aspirin-intolerant patients
Acute Stroke	
	Thrombolytic candidates: tPA 0.9 mg/kg (maximum 90 mg) with ten percent of the dose given in one minute
	Embolic stroke: anticoagulation with heparin after 12-24 hours in patients with no significant hemorrhage
	All others: aspirin 160 mg/day or clopidogrel in aspirin-intolerant patients

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

Table 21.2. NINDS trial criteria for tPA

Patients Must Have All the Following

An ischemic stroke with a clearly defined time of onset,
A deficit measurable on the NIHSS (National Institutes of Health Stroke Scale), and
Baseline computed tomographic (CT) scan of the brain showing no evidence of intracranial hemorrhage.

Exclusions (Any of the following)

Stroke or serious head trauma within the preceding 3 months;
Major surgery within the prior 14 days;
History of intracranial hemorrhage;
Systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg;
Rapidly improving or minor symptoms;
Symptoms suggestive of subarachnoid hemorrhage;
Gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days;
Arterial puncture at a noncompressible site within the previous 7 days;
Seizure at the onset of stroke;
Patient on oral anticoagulants with INR >1.7;
Patients on heparin within the previous 48 hours and still with an elevated aPTT;
Platelet count below 100,000;
Prothrombin time higher than 15 seconds;
Glucose concentration below 50 mg/dl or above 400 mg/dl.

N Engl J Med 1995; 333(24):1581-7.

Patients who do *not undergo thrombolytic therapy* and do not have an obvious embolic source for their stroke should be started on aspirin. Two large trials have shown a small but real benefit of aspirin in preventing death or disability. Since patients with stroke also have risk factors for ischemic heart disease the aspirin will be of benefit for this as well. Clopidogrel can be substituted in the aspirin-intolerant patient. Currently the combination of aspirin and clopidogrel is being examined in a large trial to see if it has any advantage over single drug therapy.

Recently a trial using a novel sustained-release form of dipyridamole and aspirin showed greater benefit in secondary stroke prevention than with aspirin alone. However, the results of this isolated trial have been controversial and in this trial the combination pill had no effect on cardiovascular events. Until further data is available from an ongoing trial, the role of dipyridamole in stroke prevention remains unknown.

Patients who clearly have an *embolic source* for their stroke require life-long anticoagulation. The timing of the initiation of heparin therapy is controversial, but patients with small strokes without significant hemorrhage should be started on heparin within 24 - 48 hours of the event and maintained on warfarin at an INR of 2-3.

It is not clear how long the patient who suffers an intracranial hemorrhage on warfarin should remain off this drug. Recent data suggest that one to two weeks off warfarin may be appropriate if the patient has a very strong indication for anticoagulation such as a mechanical valve. One should carefully investigate the circumstances around the time of the bleed to see if there are any reversible factors such as a very high INR. Given the lack of data, treatment should be tailored to the individual patient's circumstances.

A frequent cause of morbidity and mortality in the stroke patient is deep venous thrombosis and pulmonary embolism. Stroke patients should receive prophylaxis with low molecular weight heparin which has been shown to be safe and effective in these patients and does not increase the risk of bleeding.

Transient Ischemic Attacks

Patients with a transient neurological syndrome should be evaluated for the presence of carotid stenosis. Patients with ipsilateral carotid stenosis of over 70% should receive endarterectomy if they are surgical candidates. All patients with TIA should be started on aspirin. Clinical trials have shown that 30-75 mg of aspirin is equivalent to higher doses in secondary prevention. For patients who are intolerant of aspirin or who are aspirin failures clopidogrel is of benefit. Patients with atherosclerosis should also receive aggressive treatment of risk factors such as adverse lipid profiles and smoking.

Patients with Recurrent Strokes

Except for a small effect of aspirin, there is no good strategy for secondary prevention of nonembolic stroke. Patients who fail antiplatelet therapy are often placed on warfarin. Warfarin at high INRs (3-4.5) is associated with a high rate of intracranial bleeding and should not be used. A trial looking at lower INRs (1.4- 2.8) also demonstrated that warfarin fails to offers any benefit over aspirin in the secondary prevention of non-embolic strokes. Currently a clinical trial is underway to see if warfarin at an INR 2-3 is effective for stroke prevention. As noted above, trials are ongoing to study novel approaches to antiplatelet therapy.

Patent Foramen Ovale and Stroke

Patent foramen ovale (PFO) exists in 20% of normal individuals and the incidence in young stroke patients, especially those with idiopathic stroke, may be as high as 60%. Much controversy exists over the value of diagnosing PFO and approach to management. In general the PFO is more likely to be a source of embolism if:

- There is no evidence of atherosclerosis;
- There is a source of venous thrombosis;
- MRI shows areas of multiple infarcts;
- The PFO shows significant shunting;
- There is the presence of atrial septal aneurysm.

Management options for PFO are to 1) close the PFO either surgically or with catheter devices, 2) use aspirin, or 3) use warfarin. Presently there is much interest in transcatheter closure devices. However, studies demonstrate a residual risk of thrombosis and if the patient has an underlying hypercoagulable state, closure alone is not adequate therapy. Although data is conflicting, a meta-analysis has demonstrated warfarin still should be considered for patients with presumed embolic stroke and PFO.

Stroke in Young Patients

Patients under age 50 with a stroke should receive aggressive evaluation (Table 21.3). In younger patients, premature atherosclerosis and embolism are still the two most common causes of stroke. Patients should undergo a transesophageal echocardiogram to investigate for any underlying cardiac source of stroke.

Table 21.3. Evaluation of the young patient with stroke

- Angiogram
- Antiphospholipid antibodies
- Lipoprotein (a)
- Plasma homocysteine
- Transesophageal echocardiogram

Management of patients who have an embolic source of stroke and abnormalities on echocardiography is still controversial. The rate of recurrent stroke in patients with patent foreman ovale is approximately 1-2% per year. Therapeutic options include surgical correction or life-long anticoagulation. Patients with large defects, more than one event, or posterior circulation events appear to be at higher risk of recurrence.

Patients with premature strokes should receive a limited evaluation for hypercoagulable states. There is no convincing evidence that deficiency of protein S, protein C, antithrombin or the presence of the factor V Leiden mutation increases risk of stroke. Patients should be evaluated for the presence of antiphospholipid antibodies, obtain a full lipid profile and have a homocysteine level determined. Given the association with premature atherosclerosis, levels of lipoprotein(a) should also be determined.

Peripheral Vascular Disease

Acute Ischemia

Patients who present with an acute occlusion of the arterial blood supply of a limb require rapid intervention to save the limb. The time window is only four to six hours from onset of ischemia for limb salvage. Patient may suffer either an embolism or sudden thrombosis of a pre-existent atherosclerotic area. Patients with embolic disease often just require removal of the thrombus. Patients with thrombosis over atherosclerosis often require re-vascularization; therefore, differentiating between these two entities is important in order to formulate therapy. Patients who have embolic occlusion have sudden onset of symptoms and rarely have pre-existing symptoms. Often there will an obvious source of the embolism such as atrial fibrillation. Patients with underlying atherosclerosis will have previous symptoms of peripheral vascular disease.

The presentation of acute ischemia is the classic "Five P's": **P**ain, **P**allor, **P**aralysis **P**aresthesia, and **P**ulselessness. The affected limb should undergo evaluation to determine the degree of ischemia. Patients with mild weakness and sensory loss but without profound paralysis of the limb need emergent therapy to salvage the limb. The patient should undergo rapid evaluation for systemic disease. Although embolic occlusion can often be diagnosed on clinical grounds, angiography is indicated in many cases to determine the underlying cause by either demonstrating diffuse atherosclerotic disease or a discrete embolism.

Patients with acute ischemia require rapid anticoagulation with heparin. Patients with embolic disease and salvageable limbs require embolectomy via a Fogarty catheter. Catheter- based thrombolytic therapy is required for thrombi that cannot be removed with the catheter or for multiple small vessel thrombi. Patients with embolic

occlusion require anticoagulation with warfarin to an INR of 2-3 to prevent further embolic events.

Patients who have sudden thrombotic occlusion which affects limb viability either require surgical revascularization of the affected limb or thrombolytic therapy to re-open the occluded vessel. The choice of therapy is still controversial and requires consideration of the patient's vascular anatomy and surgical risk. Thrombolytic therapy is performed using intra-arterial urokinase which is infused starting at 4000 units/minute for four hours, then 2000 units/minute for up to 44 hours. Patients who reperfuse the limb after thrombolytic therapy often require either angioplasty or surgical re-vascularization due to the severity of underlying vascular disease.

Critical ischemia is signalled by rest pain. Pain is worsened by elevating the limb and may be relieved by putting the limb below the level of the heart. Patients most often require surgical revascularization to prevent tissue breakdown. Temporary control of symptoms may be achieved by a several day course of heparin therapy.

Chronic ischemia is by far the most common symptom of peripheral vascular disease, and with proper attention most patients will not progress to surgery. Patients with chronic ischemia due to peripheral vascular disease are at a higher risk of death from all vascular causes. Theses patient should receive full anti-atherosclerotic therapy, including help with smoking cessation and anti-lipid therapy. Smoking is the major risk factor for peripheral vascular disease and its progression. The other effective therapy is a supervised exercise program. Patient who follow such a program will have improvement of their exercise performance and a prolonged pain-free walking distance.

Blue Toe syndrome is a distinct syndrome with the appearance of one or more blue toes. The differential of these lesions is large (Table 21.4). The first step is to evaluate the patient for underlying diseases. Most causes of blue toe syndrome are associated with an underlying disease process and this can greatly aid in narrowing the differential. An atherosclerotic plaque that is "showering" fibrin-platelet emboli is the most common cause of blue toes in many series. These patients have underlying atherosclerosis and may have unilateral lesions. Patients with cholesterol embolization often (but not always) will have an "instigating" event such as recent catheterization that sets off a shower of emboli. These patients also may have livedo reticularis and renal dysfunction. Patients rarely may develop blue toes during the first several weeks of warfarin therapy. This is felt to be due to disruption of plaque surfaces leading to cholesterol embolization.

Therapy is dictated by the underlying disease. Patients with fibrin-platelet embolism often respond to antiplatelet therapy although definitive therapy of the vascular lesion is often required. Patients with warfarin blue-toe syndrome respond to heparin anticoagulation.

Antithrombotic Therapy for Peripheral Vascular Disease

The first-line of therapy for all patients is antiplatelet therapy with either aspirin or clopidogrel. Patients with peripheral vascular disease are at high risk for myocardial infarction and stroke in addition to their peripheral vascular diseases and these processes will also benefit from antiplatelet therapy.

Data suggests that patients undergoing femoropopliteal bypass surgery using prosthetic grafts should be started on warfarin INR 1.4 - 2.8 and aspirin 81mg - 325mg/day pre-operatively.

Table 21.4. Blue toe syndrome (after O'Keefe)

Atheroembolism	**Hypercoagulable States**
Platelet aggregates	Malignancy
Cholesterol crystals	Diabetes
Warfarin-related cholesterol embolism	Antiphospholipid antibodies
Cardiac Embolism	Essential thrombocytosis
Infective endocarditis	Erythromelalgia
Non-thrombotic endocarditis	Disseminated intravascular coagulation
Cardiac myxoma	Deep venous thrombosis
Atrial fibrillation	**Vasculitis**
Prosthetic valve embolism	Microscopic polyarteritis
Hyperviscocity Syndromes	Classic polyarteritis nodosa
Cryoglobulinemia	Lupus vasculitis
Cryofibrinogen	
Cold agglutinins	
Polycythemia rubra vera	
Leukemias	
Macroglobulinemia	

Patients who have thrombosed their bypass grafts are often treated with warfarin anticoagulation with or without aspirin. Patients whose grafts fail due to thrombosis and not due to technical reasons or fibrous hyperplasia should be given a trial of warfarin combined with low-dose aspirin.

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CHAPTER 22

Heparin and Heparin-Like Drugs

Heparin functions as an antithrombotic agent by binding antithrombin (AT), promoting inactivation of the active serine proteases involved in blood coagulation (factors IIa, VIIa-TF, IXa, Xa, and XIa). Heparin is a blend of saccharide polymers ranging in molecular weight from 3-30,000 daltons. A specific pentasaccharide sequence is required for promoting AT activity. This sequence is found in only one-third of the heparin molecules in the heparin currently used. Other polymers found in heparin may have platelet-inhibitory effects or fibrinolytic effects.

The low molecular weight heparin (LMW heparin) compounds are derived by breaking up either enzymatically or chemically the long heparin chains into smaller fragments. They have greater specific antithrombotic activity and less antiplatelet activity. They also have the virtue of being easier to dose and are safer to use. LMW heparin is the treatment of choice over standard heparin for most thrombotic disease.

The pentasaccharides are synthetic molecules which bind to antithrombin promoting its ability to inactivate factor Xa. Currently one, fondaparinux, is marketed and several more are in clinical development.

Antithrombotic Use of Low Molecular Weight Heparin

These are derivatives of heparin with improved anti-Xa effect and less antiplatelet effect (Table 22.1). Several trials have shown that the LMW heparins have an improved risk-benefit ratio over regular heparin. Since LMW heparin does not bind to acute phase proteins or endothelial cells, its pharmacokinetics are more predictable than that of standard heparin. For prophylactic use, LMW heparins can be administered once or twice daily without the need for laboratory monitoring. There is now abundant evidence that using LMW heparin for therapy in DVT/PE treatment is both safer and more effective than standard heparin. Evidence is also clear that stable patients with DVT/PE can be treated at home with LMW heparin.

Table 22.1. Standard heparin vs. low molecular weight heparin

Standard Heparin	Low Molecular Weight Heparin
Binds non-specifically to plasma proteins	Lacks non-specific binding
Increased plasma half-life with increased dose of drug	Stable plasma half-life
Binds platelet factor 4	Does not bind platelet factor 4
In therapeutic use must follow aPTT	Most patients can be treated without levels
aPTT used to monitor	Need specific plasma levels
Neutralized by protamine	Only 50% neutralized by protamine
Short half-life	Longer half-life

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Table 22.2. Agents and dosing

Heparin
Route of administration: Subcutaneous or intravenous
Prophylactic: 5,000 units tid
Therapeutic: Bolus 5-10,000 units followed by 1-2,000 units/hour to achieve heparin levels of 0.35-0.7 anti-Xa units

Low Molecular Weight Heparin

Daltaparin
Prophylactic: 2500 units qday (low risk); 5000 units q day (high-risk abdominal surgery)
Therapy: 100 units/kg every 12 hours

Enoxaparin
Prophylactic: 40 mg/day or 30 mg every 12 hours (orthopedic indications)
Therapy: 1 mg/kg every 12 hours or 1.5 mg/kg in low risk patients

Nadroparin
Prophylactic: 2850 units every 24 hours (38 units/kg in high risk patients)
Therapy: 86 units/kg every 12 hours or 171 units/kg every 24 hours

Tinzaparin
Prophylactic: 3500 units every 24 hours (4500 units in high risk patients)
Therapy: 175 units every 24 hours

Pentasaccharide

Fondaparinux
Prophylaxis: 2.5 mg every 24 hours
Therapy: 7.5 mg every 24 hours (consider 5.0 mg in patients under 50kg and 10 mg in patients over 100 kg)

For acute venous thrombosis the approved doses are either enoxaparin 1 mg/kg every 12 hours or tinzaparin 175 μ/kg every day (see Table 22.2 for all LMWH doses). For low-risk patients (calf vein thrombosis, upper extremity thrombosis), once-a-day therapy with 1.5 mg/kg of enoxaparin can be used, but this may not be adequate for higher-risk patients and twice a day therapy should be used. One trial did demonstrate that once daily dalteparin was inferior to twice a day therapy for venous disease and this dosing should not be used. For short courses of therapy, most patients do not need to have LMW heparin levels drawn. Patients who are very obese (>two times ideal body weight), who have severe liver or heart failure, who are pregnant, or on long-term LMWH therapy should have levels performed.

LMWH are renally cleared and the dose needs to be adjusted for renal function. For patients with creatinine clearance between 10-30 cc/hr the dose of enoxaparin is 0.65 mg/kg q12 hours. In patients on dialysis or with creatinine clearances less that 30 cc, the dose of enoxaparin should be 1 mg/kg/day. The pharmacokinetics of LMWH are not affected by weight and there should be no capping or adjusting of doses for overweight patients. Levels are drawn four hours after injection and the therapeutic range for enoxaparin is 0.7-1.2 anti-Xa units. Therapeutic ranges for other low molecular heparins have not been as well established.

The LMW heparins can be used in either inpatient or outpatient settings. Although LMW heparin is more expensive, inpatient savings can be realized since multiple aPTT's, daily platelet counts, and continuous intravenous therapy are not needed. In addition, it was in the general inpatient population that clinical trials demonstrated LMW heparin's effectiveness and safety over that of standard heparin.

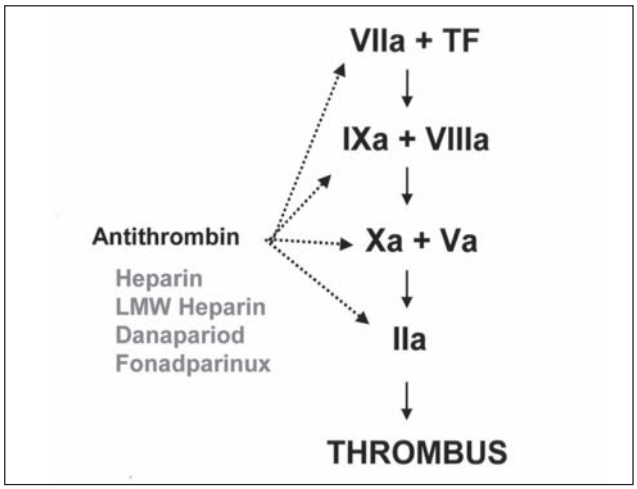

Fig. 22.1. Mechanism of actions of heparin and heparin like anticoagulants.

The ability to give LMW heparin subcutaneously has opened the door to outpatient therapy. Careful patient selection is crucial. Patients should be considered for outpatient therapy if the only reason for admission was giving intravenous heparin therapy. The first dose of LMW heparin is given as soon as possible after diagnosis, and warfarin is started the first evening after diagnosis. The second dose of LMWH should be a "transition" to get the patient on an 8am & 8pm schedule. This is derived by multiplying the patient's usual dose of 1 mg/kg by the time of the first dose until the second subtracted from 12. For example, if a 60 kg patient received his first dose at midnight, at 8am the patient would get 40 mg and from then on 60mg every 12 hours. Patients should be followed every day with a visit or phone check. One still needs to overlap LMW heparin and warfarin by 24 hours once the INR is therapeutic.

Antithrombotic Use of Standard Heparin

Standard heparin is fading from use due to its unfavorable and unpredictable pharmacokinetics. If standard heparin is used, it is critical to give enough. The strongest predictor of repeat thrombosis is failure to achieve adequate anticoagulation at *24 HOURS*. The bolus should be 5,000 units (10,000 for larger thrombi or pulmonary embolism). The initial drip should be *1400* units/hr. The traditional regimen of starting with 1000 units/hour resulted in woefully inadequate anticoagulation in the vast majority of patients. The aPTT is checked 6 hours after the bolus and the drip is adjusted accordingly if the aPTT is subtherapeutic. Since a supratherapeutic aPTT may just reflect the bolus, one should never turn down the drip until two consecutive aPTT's are supratherapeutic 6 hours apart. Therapeutic range varies with different aPTT reagents and must be standardized at each laboratory with heparin levels. A national survey showed that therapeutic heparin levels can vary from aPTT ratios of 1.8-2.5 to 2.5-4.8! Some patients may require as much as 2,000 to 2,400 units/hour.

When using standard heparin, one must be very aggressive in rapidly achieving a therapeutic aPTT. Unlike the relationship of subtherapeutic heparin levels to recurrent thrombosis, there is no association between supratherapeutic aPTT's and bleeding. Thus, one should not overreact to high aPTT values. Recently, several nomograms have been published for adjusting heparin to achieve therapeutic anticoagulation. If a nomogram is used, it must be calibrated for the particular aPTT reagent used in your lab and not simply copied from a book.

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Duration of therapy with any heparin can be as short as five days for patients with deep venous thrombosis, assuming that the patient has been adequately anticoagulated with warfarin at that time for at least 24 hours. Patients with a large pulmonary embolism should have ten days of heparin therapy since it has not yet been proven that five days is adequate. Heparin should be stopped only after the INR has been in the therapeutic range for 24 hours.

Antithrombotic Use of Pentasaccharides

One pentasaccharide, fondaparinux, is approved for use in DVT prevention with hip and knee replacement. The agent is renally cleared and should not be used in patients with renal insufficiency. Also, given the fixed dose (2.5 mg), it should not be used in patients weighing under 50 kilograms. Studies for DVT/PE therapy have been performed using the dose of 7.5 mg daily (5.0 mg in patients under 50 kg and 10 mg in patients over 100 kg). The relative effectiveness of this agent vs LMWH is still controversial but studies clearly indicated for both treatment and prevention of DVT/PE these agents are at least equivalent.

Special Problems

Patients with lupus inhibitors who require heparin are difficult to monitor since their aPTTs are already prolonged. One option is to use LMW heparin due to its predictable dosing. The other choice is to directly assay for heparin by measuring its ability to inhibit factor Xa. This assay is insensitive to lupus inhibitors. Therapeutic range for standard heparin is 0.35 - 0.7 anti-Xa units. Heparin assays are also valuable in patients where an acute-phase inflammatory process may lead to nonspecific heparin binding to inflammatory proteins, resulting in the aPTT not reflecting heparin levels. This can be seen in patients on cyclosporin. In pregnant women the acute rise in factor VIII may also lead to a misleading aPTT; thus, one should use heparin levels to guide therapy in those patients—even with prophylactic doses of standard heparin.

The hypercoagulable state associated with malignancy (especially adenocarcinomas) may be refractory to warfarin therapy. Long-term LMW heparin is a useful alternative in these patients. Patients should have LMW heparin levels checked weekly until the dose is stable.

Pregnant women with prothrombotic states pose a special problem. Pregnancy adds to the thrombotic risk but is an absolute contraindication to warfarin therapy. The use of heparin was once also feared, but recent re-analysis of the data shows that heparin can be safely used in pregnancy. There is abundant experience with LMW heparin; it is safe and effective in pregnant women for both prophylaxis and therapy. LMW heparin does not cross the placenta and is associated with less osteoporosis than standard heparin. For therapy one should follow LMW heparin levels every 4 weeks. Experience shows that levels are more stable than with standard heparin as the pregnancy progresses.

Since pregnancy is a hypercoagulable state, a patient with additional risk factors for thrombosis should receive prophylaxis. Prophylactic doses of LMW heparin are either enoxaparin at 40 mg/day or dalteparin 5000 units q12 hours. Again, the current recommended approach is to use LMW heparin. To use standard heparin, start with 5-7,500 units of heparin q12 hours and adjust the dose to keep the heparin assay at 0.1-0.2 anti-Xa units. The plasma protein changes which occur with pregnancy render the aPTT inadequate even for monitoring prophylactic doses of heparin. After delivery the patient is on warfarin for six weeks. Warfarin is excreted in the breast milk in an inactive form and is considered safe for breast feeding.

Young pregnant women with mechanical heart valves present difficult problems. Thrombosis with both standard heparin and LMWH valve has been reported. However, the majority of the cases of valve thrombosis have been in patients who were, for unknown reasons, treated with prophylactic and not therapeutic doses of heparin. At this time the best approach to treatment is unknown. Options include using standard heparin via continuous infusion pump using heparin levels to monitor therapy, LMWH at doses guided by levels, or use of heparin early, switching to warfarin mid-pregnancy, and then switching back to heparin at 36 weeks.

Complications of Heparin

Bleeding

Approximately 5% of patients placed on therapeutic heparin will bleed. Some patients appear to be more at risk than others. Patients without risk factors for bleeding have a complication rate of 1%, whereas those with risk factors have rates of bleeding of 10-23%. Risk factors include use of aspirin, age greater than 60, liver disease, and other severe illness (cancer, heart disease). The risk of bleeding is small in patient receiving prophylactic heparin. Multiple double-blind trials have shown no increase in major or fatal bleeding with the use of prophylactic heparin.

Protamine is used to reverse heparin and low molecular weight heparin. The dose for heparin reversal is dependent on timing of the last heparin dose. For immediate reversal (30 minutes or less since the last heparin dose) 1 mg of protamine should be given for every 100 units of heparin. A suggest nomogram is given in Table 22.3. One should avoid giving over 50 mg of protamine at one time and ensure that the infusion does not exceed 5 mg/min.

Protamine does not fully reverse low molecular weight heparin. Due to the longer half-life of low molecular weight heparin, sometimes a second dose of protamine is required. The dose is 1mg per 100 units of dalteparin or tinzaparin or 1 mg of protamine per mg of enoxaparin. If the aPTT is prolonged 2-4 hours later, one-half of the initial dose of protamine should be given.

Heparin-Induced Thrombocytopenia (HIT)

HIT is caused by the formation of antibodies directed against the complex of heparin bound to platelet factor 4. These antibodies then bind to the platelet Fc receptor and activate the platelet. Thus, the thrombocytopenia of HIT is due to platelet activation and deposition and not immune destruction. The frequency of HIT is 1-5% when unfractionated heparin is used but less than 1% with low molecular weight heparin. HIT should be suspected when there is a sudden onset of thrombocytopenia defined as either 40% or greater reduction in the platelet count, or the platelet count falling to less than 100,000/uL in a patient receiving heparin in

Table 22.3. Agents for HIT

Argatroban
Therapy: initial dose of 2 μg/kg/min adjusted to an aPTT of 1.5-3.0 times normal.

Bivalirudin (PCI dosing)
Bolus: 1 mg/kg
Infusion: 2.5 mg/kg/hour for 4 hours and then 0.2 mg/kg/hour for 14-20 hrs.
For renal adjustment see Chapter 23

Danaparoid
Therapeutic: bolus of 2250 units (1500 units <60 kg, 3000 units 75-90 kg, 3750 units > 90kg), then a four-hour infusion of 400 units/hour, then 4 hours of 200 units/hour, then a drip at 150-200 u/h to maintain an anti-xa level of 0.5-0.8 anti-xa units.

Fondaparinux
Prophylaxis: 2.5 mg every 24 hours
Therapy: 7.5 mg every 24 hours (consider 5.0 mg in patients under 50 kg and 10 mg in patients over 100 kg)
Use with caution in patients with renal insufficiency

Hirudin
Therapy: bolus of 0.4 mg/kg followed by 0.15 mg/kg/hour to maintain an aPTT of 1.5-3.0 times normal.
For renal adjustment see Chapter 23

any form. HIT usually occurs 5-10 days after starting heparin but may occur suddenly in patients rechallenged with heparin with recent (less than 3 months prior) exposure. An often overlooked presentation of HIT is recurrent thrombosis in a patient receiving heparin despite a normal platelet count. Often when the heparin is stopped the platelet count rises to above normal levels. Another unique presentation of HIT is thrombosis occurring up to 2 weeks after heparin exposure. The patients present with thrombosis, thrombocytopenia, and 25% will also have laboratory evidence of disseminated intravascular coagulation.

The clinical diagnosis of HIT can be challenging, especially in the very sick patient who has multiple reasons for being thrombocytopenic. In this situation the laboratory assay for HIT may be helpful. Two general forms of HIT tests exist. One is a platelet aggregation assay where patient plasma, donor platelets, and heparin are mixed. If added heparin induces platelet aggregation the test is considered positive. The test is technically demanding but if performed carefully can be sensitive and specific. One caveat is that early in the HIT disease process the test can be negative but then turns positive 24 hours later as the antibody titer increases. There is also an ELISA assay for the presumed pathogenic anti-platelet factor 4 antibodies. This test tends to be too sensitive but can also miss up to 20% of HIT due to antibodies other than anti-platelet factor 4 antibodies; the test is not clinically useful.

Recently Warkentin has developed a scoring system for HIT (Table 22.4). Patients with high pre-test probabilities should be treated for HIT no matter what the laboratory testing demonstrated. Lab tests are most helpful for patients with intermediate probability of HIT. Platelet aggregation tests can also be useful in diagnosis low probability patients with HIT but the ELISA assay may be too sensitive in these patients.

The first step in therapy of HIT consists of stopping all heparin. Two particular problems in the critical care setting are that many catheters are kept open with

Table 22.4. Heparin induced thrombocytopenia scoring system

Points	**2**	**1**	**0**
Thrombocytopenia	>50% fall or nadir 20-100,000/ul	30-50% fall or nadir 10-19,000/ul	Fall < 30% or nadir <10,000/ul
Timing of platelet fall	Onset day 5-10 of heparin or < 1 day if patient recently exposed to heparin	consistent but not clear records or count falls after day 10	platelets falls < 5 days and no recent (100 days) heparin
Thrombosis	New thrombosis or skin necrosis or systemic reaction with heparin	Progressive or recurrent thrombosis or suspected but not proven thrombosis	None
O**T**her cause for thrombocytopenia	No	Possible	Definite

Pretest Score 6-8=high, 4-5 intermediate, 0-3 low
Warkentin, Heddle Current Hematology Reports 2:148; 2003.

heparin and can be a hidden source of heparin for patients with HIT. Also, many central venous catheters and intra-aortic balloon pumps are coated with heparin. The presence of heparin-coated catheters is enough to perpetuate the HIT process, and these must be changed to non-heparin coated devices.

Patients with HIT and active thrombosis are difficult to manage since these patients cannot receive heparin. Low molecular weight heparins cross-react with the HIT antibodies and therefore these agents are also contraindicated. Institution of warfarin therapy alone has been associated with an increased risk of thrombosis. Several antithrombotic agents are now available for immediate therapy of HIT (see Table 22.3).

Argatroban is a synthetic thrombin inhibitor. It has a short half-life of 40 minutes. Dosing is 2 μg/kg/min with the infusion adjusted to keep the aPTT 1.5-3 times normal. Although not widely available, more precise monitoring of argatroban and other thrombin inhibitors may be obtained by using either the ecarin time or the quantitative thrombin time. One advantage of argatroban is that it is not renally excreted and no dose adjustment is necessary in renal failure. These characteristics make it the most useful agent for patients in the critical care unit. However, argatroban must be used with caution in patients with severe liver disease (initial dose of 0.5 μg/kg/min and titrate upward). Argatroban, like all thrombin inhibitors, prolongs the PT-INR, making initiation of warfarin therapy difficult. If available, the chromogenic X assay may be used to adjust warfarin therapy. Also, if the patient is on a drip of 2 μg/kg/min or less, one can simply aim for a PT-INR of more than 4.0 as therapeutic. Once the drip is stopped, one should measure the PT-INR in 4-6 hours to ensure it is in the therapeutic range. Unfortunately there is no agent that can reverse argatroban, but given its short half-life this is most often not a problem.

Lepirudin, another direct inhibitor of thrombin, is also monitored by using the commonly available aPTT. The half-life of lepirudin is short, but the drug accumulates in renal insufficiency with the half-life increasing to more than 50 hours. There is no antidote for lepirudin. Patients with even slight renal insufficiency (creatinine greater than 1.5) must have lepirudin doses adjusted to avoid over-anticoagulation.

Up to 80% of patients receiving long- term lepirudin therapy will develop antibodies. These antibodies reduce the metabolism of hirudin and *increase* the therapeutic effect of lepirudin. In addition, rare cases of anaphylaxis have been reported. Patients on long-term (> 6 days) lepirudin therapy should still continue to be monitored to avoid over-anticoagulation.

Bivalirudin has been reported in limited studies to also be effective in HIT. However, like lepirudin, bivalirudin needs dose adjustment in renal disease. There is also concern about antibody formation since anti-lepirudin antibodies can cross react with bivalirudin.

Also available is danaparoid, a mixture of various glycosaminoglycans. Unfortunately its half-life is 25 hours, there is no antidote, and monitoring must be done by specific danapariod levels. These factors greatly limit the use of this agent. One useful aspect of danapariod is that it can be given as twice a day injections of 2500 units and is useful for the rare patient with HIT who cannot take warfarin but needs long-term anticoagulation.

The new anti-Xa inhibitor fondaparinux does not cross-react with HIT antibodies. Fondaparinux may be useful for DVT prophylaxis in patients with a history of HIT and, as clinical experience accumulates, for therapy of these patients. However, its long half-life and lack of antidote remain a problem. In clinical development is ximelagatran, an oral thrombin inhibitor which may prove useful for long-term therapy of HIT patients.

As mentioned above, initiation of warfarin alone has been associated with limb gangrene, and it should not be started as the sole antithrombotic agent in HIT. In patients receiving specific antithrombin therapy, warfarin can be started with small doses (2- 5 mg). These often malnourished patients tend to have a dramatic response to warfarin therapy and excessive anticoagulation can easily occur. One should overlap warfarin and parenteral therapy by 2-3 days as there is evidence that patients may do worse with shorter durations of specific antithrombin therapy.

Patients with HIT but without evidence of thrombosis are at a high risk of thrombosis (53% in one study) and should be considered for antithrombotic therapy. Patients with HIT should also be carefully screened for any thrombosis, which includes obtaining lower extremity dopplers. It is unknown whether prophylactic doses or therapeutic doses of anticoagulants are needed for thrombosis prevention in patients with HIT but no thrombosis. The duration of such therapy is also controversial. One approach is to give prophylactic doses of antithrombotic agents until the platelet count has returned to normal. In post-surgical patients prolonged prophylaxis for up to six weeks may be of benefit.

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CHAPTER 23

Direct Thrombin Inhibitors

Introduction

Given thrombin's central role in coagulation, direct inhibition of thrombin is a potent mechanism for achieving anticoagulation. The first thrombin inhibitor, hirudin, was derived from leech saliva and it is clinically available as the recombinant product lepirudin. Also currently clinically available are argatroban and bivalirudin; ximelagatran is in clinical trials.

Thrombin inhibitors share certain properties. They raise both the INR and aPTT since thrombin is part of the common pathway of blood coagulation. Clinically they are monitored by the aPTT, usually aiming for a goal of 2-2.5 times normal control. More precise monitoring can be achieved by using the ecarin time. No effective antidote exists for these agents.

Since all thrombin inhibitors prolong the PT-INR, initiation of warfarin therapy is difficult. If available, the chromogenic factor X assay can be used to adjust warfarin therapy. This assay is not affected by the thrombin inhibitor. Warfarin is started at a low dose of 2.5-5 mg/day and a daily factor X assay is performed. When the level is down to 15-30% the thrombin inhibitor is stopped. If argatroban is used, there is a nomogram to guide warfarin therapy if doses of 2 μg/kg/min and under are used.

Argatroban

Argatroban is a synthetic thrombin inhibitor derived from L-arginine that binds only to the thrombin active site. It has a short half-life of 40 minutes. The dosing for anticoagulation is 2 μg/kg/min with the infusion adjusted to keep the aPTT 1.5-2.5 times normal. Argatroban can also be used for percutaneous coronary intervention with a bolus of 350 μg/kg being given and then a continuous infusion of 25 μg/kg/min started.

One advantage of argatroban is that it is not renally excreted and therefore no dosage adjustment is necessary in renal insufficiency or failure. These characteristics make it the most useful agent for patients who require thrombin inhibitors. However, argatroban must be used with caution in patients with severe liver disease. An initial dose of 0.5 μg/kg/min is used and titrated upward guided by the aPTT. To start warfarin in the patient on a drip of 2 μg/kg/min or less one can simply aim for a PT-INR of more than 4.0 as therapeutic. Once the drip is stopped, one should measure the INR in 4-6 hours to ensure it is in the therapeutic range.

Lepirudin

Hirudin is derived from leech saliva. It binds both the active site of thrombin and the substrate binding site. Currently hirudin is made using recombinant technology.

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Table 23.1. Argatroban, hirudin and bivalirudin

Argatroban
- Therapy: 2 μg/kg/min infusion with dose adjustments to keep aPTT 1.5 - 3 times normal.
- For patients with severe liver disease, start with 0.5 μg/kg/min infusion and follow aPTT to same goal of aPTT 1.5 - 3 times normal.
- For PCI:
  - Bolus with 350 μg/kg over 3-5 minutes and then infuse with a maintenance drip of 25 μg/kg/min adjusting to a ACT of 350-400 minutes.

Hirudin
- Therapy: bolus of 0.4 mg/kg followed by 0.15 mg/kg/hour to maintain an aPTT of 1.5-3.0 times normal.
- Adjustments for Renal Dysfunction:
  - For creatinine of 1.6-2.0 mg/dl: bolus of 0.2 mg/kg followed by a 50% reduction in infusion rate.
  - For creatinine of 2.0-2.5: bolus of 0.2 mg/kg followed by a 75% reduction in infusion rate.
  - For creatinine of 2.6-6.0:bolus of 0.2 mg/kg followed by a 90% reduction in infusion rate.
  - For creatinine of greater than 6.0 mg/ml: Bolus of 0.1 mg/kg on alternate days only when the aPTT is less than 1.5 times normal; no continuous infusion.

Bivalirudin
- Bolus: 1 mg/kg
- Infusion: 2.5 mg/kg/hour for 4 hours and then 0.2 mg/kg/hour for 14-20 hrs.
- Renal adjustment:
  - For creatinine clearance of 30-59 ml/min, decrease dose by 20%
  - For creatinine clearance of 10-29 ml/min, decrease dose by 60%
  - For creatinine clearances less than 10 mg/min, decrease dose by 90%

Ximelagatran
- DVT prophylaxis: 24 mg po BID
- Therapy of DVT: 36 mg po BID
- Stroke prevention in atrial fibrillation: 36 mg BID

Lepirudin, like all thrombin inhibitors, is also monitored by using the commonly available aPTT. The half-life of lepirudin is short, but the drug accumulates in renal insufficiency with the half-life increasing to up to more than 50 hours. Patients with even mild renal insufficiency (creatinine greater than 1.5) must have lepirudin doses adjusted to avoid overanticoagulation. Up to 80% of patients receiving long-term lepirudin therapy will develop antibodies. These antibodies reduce the metabolism of hirudin and *increase* the therapeutic effect of lepirudin. Patients on long-term (greater than 6 days) lepirudin therapy should still continue to be monitored to avoid over-anticoagulation. Rare cases of anaphylaxis have been reported. Lepirudin has also been used for anticoagulation for myocardial infarctions and as an adjunct to PCI.

Bivalirudin

Bivalirudin is a synthetic thrombin inhibitor that binds to the thrombin active site and also to the substrate binding site. It also has a short half-life of 30 minutes. Its use is best studied for cardiac indications and it is currently approved for PCI. Bivalirudin is also renally excreted and dosage adjustments should be made

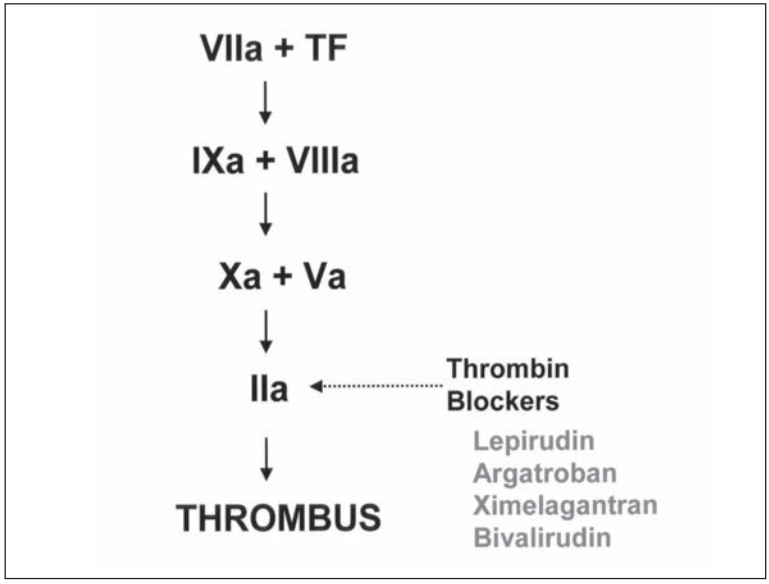

Fig. 23.1. Mechanism of action of thrombin inhibitors.

for patients with renal insufficiency. In theory, bivalirudin should be useful for heparin induced thromocytopenia (HIT) but it has not been clinically studied for this indication.

Ximelagatran

A novel agent in clinical development is ximelagatran. This agent is a prodrug of the thrombin inhibitor melagatran. This drug is orally available and has a half-life of 2.5-3.5 hours. The agent is renally metabolized and dosage may need to be adjusted for renal insufficiency. Unlike warfarin, ximelagatran metabolism is not effected by food, drugs, or age. Clinical trials have shown that ximelagatran (24 mg bid) is as effective for prophylaxis in surgery that is high risk for venous thrombosis prophylaxis. Data shows that a therapeutic dose of 36 mg bid is just as effective as warfarin in prevention stroke in patients with atrial fibrillation. Clinical trials have also demonstrated that ximelagatran along is just as effective as enoxaparin followed by warfarin in the therapy of DVT/PE. The major side effect of ximelagatran is elevations in liver function tests that occur in 3-6% of patients starting this drug. Most patients can continue the drug but it is unknown what is the best protocol for monitoring patients and if rare patients will develop severe drug induced hepatitis.

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CHAPTER 24

Warfarin

Warfarin works by interfering with vitamin K-dependent gamma-carboxylation of coagulation proteins II, VII, IX, and X. As a result of warfarin therapy, these coagulation factors cannot bind calcium. This causes impairment of these factors' binding to membranes and to fold into proper configuration. Therapy with warfarin is initiated by giving the patient 5-10 mg in the evening for the first two nights (2.5 mg in those over 75 years) and adjusting the dose to achieve an adequate prothrombin time. Although the use of a 10 mg loading dose has been traditional in the past, for most people this is too much. Multiple trials show that using a 10 mg loading dose causes one to overshoot and leads to a delay in achieving a stable therapeutic INR. A practical approach is to use 5mg in loading patients over the age of 50 or in patients with albumin under three and 10 mg in other patients. The elderly patient (over age 75) may only need a 2.5 mg loading dose. Nomograms for 5 and 10 mg warfarin loading doses are given in Table 24.1. The effect of warfarin on the INR takes 36 hours to occur so the morning INR reflects the effect of the warfarin dose 36 hours before.

Factor VII has the shortest half-life and so it is the first factor reduced as a result of warfarin therapy. However, the full anticoagulant effect does not occur until there is a reduction in prothrombin (factor II) and factor X, which may take several days. Thus, in acute thrombosis heparin needs to be continued for at least 24 hours after the prothrombin time is therapeutic to allow for factors II and X to fall. For chronic indications such as atrial fibrillation, warfarin can be started at lower daily doses (2.5-5.0 mg). This allows for initiation of warfarin therapy without the use of heparin. Table 24.2 gives guidelines for adjusting warfarin doses in patients once therapeutic prothrombin times have been reached.

Unfortunately the dose of warfarin required for achieving therapeutic anticoagulation varies among patients. This is due to a combination of the patient's genetic ability to metabolize warfarin, concurrent medications and illnesses, and diet. Patients who are older require less warfarin, with patients over age 65 requiring one-half to one-third of the warfarin doses of younger patients. Also variations in cytochrome 2C9 (CYP2C9) can affect warfarin metabolism. The most common genotype is 2C9*1 with 80-90% of the population carrying this allele. The 2C9*3 allele (found in 6-10%) is much less efficient in metabolism of warfarin. For example, studies have shown that 2C9*1/*1 requires an average of 3-4.25 mg/day of warfarin compared to 1.75-2.5 mg/day for 2C9*1/*3 and 0.4 mg/day for 2C9*3/*3. Studies are underway to see whether knowing the 2C9 genotype of the patient can predict warfarin dose or bleeding complications.

Since warfarin is metabolized in the liver by the cytochrome P450 system, the INR may change with starting or stopping other medications that affect CYP2C9. Multiple agents can augment or decrease warfarin effect and are listed in Table 24.3. Unfortunately, many drugs may have an unpredictable effect on the INR. The most prudent strategy is to check the INR several days after starting a new drug and then

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Table 24.1. Nomograms for warfarin loading

Day	INR	Dosage (Mg)
5 Mg Warfarin Nomogram		
1		5.0
2	< 1.5	5.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0
10 mg Warfarin Nomogram		
1	10.0	
2	< 1.5	7.5-10.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0

Crowther MA, Harrison L, Hirsh J. Ann Internal Med 1997; 127:333.

Table 24.2. Maintenance warfarin adjustment nomogram (Hatheway and Goodnight)

INR	Dose Change
1.1-1.4	Day 1: Add 10-20% total weekly dose (TWD)* Weekly: Increase TWD by 10-20% Return: 1 week
1.5-1.9	Day 1: Add 5-10% of TWD Weekly: Increase TWD by 5-10% Return: 2 weeks
2.0-3.0	No Change Return: 4 weeks
3.1-3.9	Day 1: Subtract 5-10% TWD Weekly: Reduce TWD by 10-20% Return: 2 weeks
4.0-5.0	Day 1: No warfarin Weekly: Reduce TWD by 10-20% Return: 1 week
> 5.0	Stop warfarin until INR <3.0 Decrease TWD by 20-50% Return daily

*TWD = Total weekly dose

weekly to ensure the INR is stable. If the patient is started on a drug which results in predictable changes in the INR, then the warfarin dose may be adjusted, usually by 50%, when starting that drug.

Vitamin K is found in many foods (Table 24.4), especially green vegetables. Patients will often avoid any vegetables due to fear of reversing their anticoagulation. This will result in those patients having lower vitamin K stores and will make them prone to unstable INRs. Patients should be instructed that *consistency* of diet is more important than avoiding vitamin K. A diet rich in vegetables and fruits is beneficial, especially for patients being anticoagulated, and should be encouraged. Patients should be advised of the vitamin K content of common foods and should be encouraged to be consistent with their diet.

Therapeutic Range of INR

Warfarin therapy is guided by the prothrombin time. Separate laboratories use thromboplastin from different manufacturers which results in variability of the prothrombin time. The International Normalized Ratio (INR) is the prothrombin time ratio that would be obtained if the "WHO reference thromboplastin reagent" was used to test the plasma. Laboratories convert their local prothrombin time ratios to INRs by using the ISI (International Sensitivity Index) by the formula $INR=PT\ RATIO^{ISI}$. The advantage of the INR is that it reflects a constant level of anticoagulation despite the different thromboplastins used to perform the prothrombin time. The ISI of thromboplastin used in the United States ranges from 1.4 to 2.8. Given this, an INR of 3.0 can be equivalent to a protime of anywhere from 18.1 to 26.8 seconds. Thus it is meaningless to use the prothrombin time and INR should always be used, especially when dealing with different laboratories.

Table 24.3. Medication effects on warfarin effect

Increased Warfarin Effect
- **Acetaminophen**
- Allopurinol
- **Amiodarone*** (may last for months after drug is stopped)
- Anabolic steroids*
- **Aspirin***
- Cephalosporins (nmtt group)
- **Cimetidine***
- Clofibrate*
- Cyclophosphamide
- **Disulfiram**
- **Erythromycin***
- **Fluconazole***
- Furosemide
- Gemfibrozil
- Isoniazid
- **Itraconazole***
- **Ketoconazole***
- **Metronidazole***
- **Micronase***
- Omeprazole
- **Propafenone**
- Propranolol
- Quinidine*
- Quinine*
- Quinolones
- Serotonin re-uptake inhibitors
- **Sulfinpyrazone***
- Sulfonylureas*
- Tamoxifen*
- Tetracycline*
- **Thyroid hormones***
- Tricyclic antidepressants
- Vitamin E*

Decreased Warfarin Effect
- Alcohol
- **Barbiturates***
- Carbamazepine
- Corticosteroids
- **Phenytoin** (may potentiate warfarin at initiation of drug)
- **Cholestyramine**
- Estrogens
- **Griseofulvin**
- Rifampin
- Sucralfate
- Vitamin K

*= major effect
Drugs in bold are the most implicated in having an effect on warfarin therapy.

Table 24.4. Vitamin content of foods

Item	Vitamin K Content (μg/100 μg)
Green tea	712
Avocado	634
Turnip greens	408
Brussels sprouts	317
Chickpeas	220
Broccoli	200
Cauliflower	192
Lettuce	129
Cabbage	125
Kale	125
Beef liver	92
Spinach	89
Watercress	57
Asparagus	57
Lettuce (iceberg)	26
Green beans	14

The therapeutic INR range for most indications for warfarin is an INR of 2.0-3.0. Patients with mechanical heart valves will require higher doses of warfarin to aim for a target INR of 3-4.5. To avoid subtherapeutic doses of warfarin, it is better to aim for a "target" INR of 2.5 and use the range of 2-3 as indicating acceptable values. Use of the mid-range target as a therapeutic goal results in a lower incidence of subtherapeutic INRs.

Complications of Warfarin Therapy

Bleeding. Studies have shown that physicians consistently overestimate the risk of bleeding with warfarin. Past studies of the bleeding risk are marred by an inconsistent approach to anticoagulation, use of nonstandardized measures prior to INRs, and retrospective analysis. Newer studies have shown that the risk of bleeding with warfarin is highly dependent on several factors. The most significant risk factor is over-anticoagulation. A dramatic reduction of bleeding risk with no effect on antithrombotic efficacy occurs when lower (but still therapeutic) INRs are used as shown in Figure 3. Patients with variability of the INR resulting in frequent dose changes were also found to be at higher risk of bleeding. Patients who abused alcohol or who were being anticoagulated for arterial indications (i.e., stroke or atrial fibrillation) were at higher risk of bleeding. A higher risk of bleeding was seen during the first three months of warfarin therapy when compared with the rest of the course. Finally, patients with three or more co-morbid conditions were at higher risk.

Although age may not be a risk in and of itself, certain conditions associated with aging increase the risk of bleeding. Older patients require less warfarin to achieve the desired anticoagulation effect. Secondly, many older patients are on a variety of medicines that can interfere with warfarin. Finally, the very old (>80) may be at increased risk of intracranial hemorrhage.

Patients with GU or GI bleeding should be worked up aggressively since pathological lesions will be found in over 50% of anticoagulated patients who have this type of bleeding.

In general the risk of major bleeding with warfarin in an average patient is 1%/year; the risk of fatal bleeding is 0.2-0.25%/yr.

Warfarin Skin Necrosis. This is an extremely rare but devastating complication of warfarin therapy. Classically it starts 4 days after initiation of therapy with pain and skin discoloration. Then frank necrosis occurs in the affected area. Most common sites are the breast and buttocks in women and the penis in men. Most reported cases have occurred in post-surgical or post-partum patients with venous thrombosis. Many (but not) all patients had protein C or protein S deficiencies when tested. The etiology of the skin necrosis is still debated but it appears that protein C or S deficiency and an inflammatory state are prerequisites for occurrence. The entity has not been described in patients anticoagulated for arterial events. A prudent approach is to overlap warfarin therapy with heparin for 24 hours whenever anticoagulating patients with venous thrombotic events. When starting warfarin for arterial events or for prophylaxis in atrial fibrillation, heparin coverage is probably not required if the patient does not have a personal or family history of venous thrombosis or evidence of antiphospholipid antibodies. Warfarin should be started gradually at 2.5-5.0 mg/day in these patients.

Warfarin Resistance and Unstable INRS

Two common problems complicate warfarin therapy. One is the patient who requires large doses of warfarin and the other is the patient with erratic INRs.

Rarely, the clinician is faced with a patient in whom massive doses of warfarin are required for anticoagulation or, more disturbingly, the patient who seems to be resistant to even large doses of warfarin. A careful evaluation of such a patient is needed to determine the cause of the warfarin resistance.

True genetic warfarin resistance is extremely rare, with only four affected kindreds reported. These patients are always difficult to anticoagulate and may only respond to very large doses (i.e., 150 milligrams) of warfarin. More common is acquired resistance to warfarin. The three major causes of acquired resistance are medications, ingestion of vitamin K, and non-compliance.

It is less common for medicines to inhibit the action of warfarin than to potentiate it. Common drugs which inhibit warfarin action are barbiturates, rifampin, and nafcillin. Patients on these medications may require 20 mg of warfarin per day to maintain a therapeutic INR. Since most drug-warfarin interactions are mediated through induction of liver enzymes, it may take several days for the warfarin resistance to be noticed after starting the drug and several days for the effect to wear off after stopping the drug. Cholestyramine uniquely interferes with warfarin absorption.

Vitamin K is found in several nutritional supplements and often in generic multivitamins, and use of these products can result in warfarin resistance. For example, Ensure contains 80 μg of vitamin K per 1000 kcal and Sustacal 230 μg/1000 kcal. In patients who depend solely on these products for nutrition large doses of warfarin or anticoagulation with heparin may be required. If a patient changes supplements or starts ingesting regular food, the warfarin requirement will change dramatically. Patients may also be ingesting large amounts of vitamin K-containing food that can induce warfarin resistance. Even one or two days of high intake of vitamin K-rich food can dramatically lower INRs.

Some patients who present with warfarin resistance are simply not taking the medicine as prescribed. These patients initially require the usual doses of warfarin therapy but then present with normal INRs despite massive warfarin doses. Measur-

ing serum warfarin levels are useful in patients suspected of non-compliance. Patients with undetectable warfarin levels despite allegedly taking large doses of warfarin are most likely not taking the drug. In the patient who has a non-detectable warfarin level, a level should be repeated after the patient is witnessed taking the drug to ensure that the patient is not suffering from rare malabsorption of warfarin. One case has been described of a patient who could not absorb warfarin but could absorb phenindione, a non-coumarin vitamin K inhibitor. Curiously, this malabsorption occurred after two years of stable warfarin therapy.

Patients with erratic INRs are at greater risk for both bleeding and thrombosis. Patients need to be questioned about use of all other medications including "natural" remedies and over- the-counter medicines. A good dietary history as well as a frank discussion about compliance should be performed. Adding vegetables and other sources of vitamin K to the diet will stabilize the INR in some patients.

Correction of Warfarin Overdose (Table 24.5)

The key in approaching the patient with an elevated INR is to first determine if they are bleeding. Patients who are bleeding and have an elevated INR need an aggressive approach to reversal of their warfarin, while those just with an elevated INR can be managed less aggressively with the goal of allowing the INR to return to therapeutic range. However, the risk of bleeding in patients with an elevated INR may be substantial. A recent study showed that older patients being started on anticoagulation for cardiac disease have a risk of bleeding of 8.8% in the two weeks after presenting with an INR of greater than 6.

The cornerstone of management of a high INR is vitamin K. Often shunned, both oral and intravenous vitamin K offer significant advantages over the use of sub-cutaneous vitamin K or plasma. In fact, due to its erratic absorption and delay in INR reversal, the use of subcutaneous vitamin K is discouraged. Intravenous vitamin K, even infused slowly, is associated with a small risk of anaphylaxis (<1%) and should be reserved for life-threatening bleeding or other indications for rapid reversal. For most situations the oral route will result in more reliable results than the subcutaneous route with the onset of action within 12 hours. If speedy reversal is needed, the intravenous route should be used.

Often only small doses of vitamin K in the range of 0.5-3 mg are needed. Crowther showed that use of 1 mg orally of vitamin K in patients with INRs of 4.5-10.0 lowers the INR of 56% of patients compared to 20% of placebo patients by 24 hours and reduced the risk of bleeding from 7 to 2%.

For nonbleeding patients with INRs higher than the therapeutic range but less than 4.5, one can simply omit or reduce that day's dose. There is a delay of 24-36 hours after stopping warfarin before the INR begins to fall. For INRs in the 5-10 range one can hold the next 1-2 doses and give orally 1 milligram of vitamin K. For INRs of more than 10, one should give 2.5 milligrams of oral vitamin K with the expectation that the INR will fall in 24-48 hours.

If the patient with INR 2 - 4.5 requires rapid full reversal because of bleeding or need for surgery, one can give 2.5 milligrams vitamin K orally with the expectation that the INR will be lower in 24 hours. The intravenous route will result in shortening of the INR in as little as 4-6 hours. For INR of 4.5 -10 one can give 2.5 - 5 mg of vitamin K. For INRs over 10 one should give 5 milligrams orally or IV. For most rapid reversal of anticoagulation one should give both vitamin K and fresh frozen plasma. Since one unit of plasma on average increases levels of coagulation factors

Table 24.5. Mangagment of high INRs

Elevated INR and *NOT* Bleeding (Goal: INR back in therapeutic range)

INR	Action
3 - 4.5	Reduce weekly dose by 10-20%
4.5 - 10	1 mg po Vitamin K
>10	2.5 mg po Vitamin K

Elevated INR and Bleeding (Goal: Corrections of INR)

INR	Action
2-4.5	Give 1- 2.5 mg po or IV* vitamin K ± 15 ml/kg of plasma
4.5 - 10	Give 2.5 - 5 mg po or IV* vitamin K ± 15 ml/kg of plasma
> 10	Give 5-10 mg po or IV* vitamin K ± 15 ml/kg of plasma

Note: For intracranial hemorrhage consider either 50 units/kg of prothrombin complex concentrate or 40 μg/kg of rVIIa
* IV will work faster but carries slight risk of anaphylaxis

by only 5%, one must give large doses (15 mg/kg or 4-5 units) to attempt to correct the INR. Obviously, giving this volume of plasma in a short period of time runs the risk of volume overload.

High doses of vitamin K (greater than 5 milligrams) should only be used for life-threatening bleeding, very high INRs (greater than 20) or if for the time being the patient does not need further anticoagulation. These high doses can render the patient refractory to warfarin for a prolonged period of time.

Warfarin Reversal in the Patient with Life-Threatening Bleeding

Intracranial hemorrhage occurs in patients on warfarin at a rate of 0.2-2%/year, with the higher rates being seen in older patients and those with higher INRs. These hemorrhages are particular devastating with most patients either dying or rendered incapacitated by the bleeding.

Immediate management of bleeding is to reverse rapidly the warfarin effect. This can be done by giving both vitamin K (10 mg intravenous slowly over one hour) and 15 mg/kg of fresh frozen plasma. It is important to give the vitamin K with the plasma because the effect of plasma is only transient and the patient may have a rebound rise in the INR if vitamin K is not given.

If available, patients with intracranial hemorrhages or other life-threatening bleeding should receive prothrombin concentrates. Clinical data has shown that these products (which contain all the vitamin K-dependent clotting factors) result in a more rapid correction of coagulation than plasma. Patients suffering intracranial hemorrhage should receive prothrombin concentrates such as Konyne or Prophylnine at a dose of 50 units/kg. Unfortunately these products are not often readily available. Recent data suggests that the use of recombinant factor VIIa can reverse warfarin-induced bleeding. Data is sparse concerning the ideal dose, but 40 μg/kg given along with vitamin K should be effective

Management of the Patient on Warfarin Who Needs a Procedure

Many patients on warfarin will require surgical procedures. There is still limited clinical data on proper management of these patients. For most dental procedure

Table 24.6. Management of patient anticoagulated with warfarin who needs a procedure

Day -5:	Stop warfarin five days before procedure.
Day -3:	Start enoxaparin 1mg/kg every 12 hours.
Day -1:	Give last dose evening before surgery and hold next morning dose. If patient to receive epidural also hold the evening dose
Day 0:	Check PT-INR/aPTT morning of surgery. For most procedures can start warfarin the night of surgery. If very minor procedure restart therapeutic LMW heparin. Otherwise start prophylactic doses and change to therapeutic when safe from a surgical standpoint.

the patient does not need to stop warfarin as long as the INR is under 3. One approach is for low risk patients (last venous thrombosis over 6 months ago, atrial fibrillation without history of stroke) is to stop the warfarin 5 days before surgery to allow the INR to fall to below 1.5. For higher risk patients "bridging" therapy as outlined in Table 24.6 may be useful. Management of high risk patients after surgery should be individualized. Patents with minor procedures can be restarted on heparin/warfarin immediately while patients who undergo major procedures or where surgical bleeding could be devastating should receive prophylactic doses of LMW heparin until hemostasis has been achieved. The consulting physician should work closely with the surgeon on these cases.

Suggested Reading

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CHAPTER 25

Antiplatelet Agents

Aspirin

Aspirin is the oldest and still the most widely used antiplatelet agent. Aspirin exerts its antithrombotic effect by irreversibly inhibiting platelet cyclooxygenase through acetylation of the reactive serine. This prevents the formation of the platelet agonist thromoboxane A_2 and thereby inhibits platelet function.

In most patients, platelet cyclooxygenase can be inhibited by aspirin doses as small as 30 mg per day. In clinical trials, aspirin doses ranging from 1,200 mg to 30 mg daily have been shown to be effective for prevention of thrombosis. Gastrointestinal side-effects are diminished by the lower doses. Currently, the recommended dosage of aspirin is 80 - 325 mg/day. Aspirin is rapidly metabolized by the liver, and when the drug is taken in low doses, most platelet inhibition occurs in the portal vein. Since the platelet inhibition lasts the life of the platelet, the biological half-life of aspirin is considerably longer than the plasma half-life.

Aspirin is the initial therapy for any arterial ischemic disorder. Clinical trials have shown aspirin to be effective in ischemic heart disease, angioplasty, coronary artery by-pass surgery, and in cerebrovascular disease.

Aspirin is effective in primary and secondary prevention of myocardial infarctions. In a meta-analysis by the Antiplatelet Trialist Collaboration, aspirin use after myocardial infarction reduces the risk of non-fatal strokes by 42%, non-fatal MI by 31% and vascular death by 13%. Aspirin use in acute myocardial infarction reduces strokes by 45%, re-infarction by 49%, and vascular death by 22%.

Five clinical trials have demonstrated that aspirin is effective as primary prevention of myocardial infarction in patients with cardiac risk factors such as being over age forty, diabetes, hypertension, presence of other vascular disease, and hypercholesterolemia.

Aspirin is also effective in stroke prevention after TIA. However, endarterectomy is more effective than aspirin when internal carotid stenosis exceeds 70%. Aspirin also offers modest secondary prevention after a completed major stroke, preventing one stroke per 1,000 patients treated.

Aspirin effect is achieved very rapidly with oral ingestion of more than 160 mg; this dose should be used when a rapid antiplatelet effect is desired such as in acute myocardial infarction. Since platelet cyclooxygenase is permanently inhibited, the anti-platelet effect of aspirin will last until the majority of circulating platelets have been replaced; this may take 3-5 days.

The major side-effect of aspirin is bleeding. Minor bleeding complications are increased by 5%. Randomized trials suggest that the incidence of severe or fatal bleeding with aspirin use is increased by 0.5%/year of use with chronic use.

For a bleeding emergency in the patient taking aspirin, platelet transfusions can be given. The half-life of circulating aspirin is short, especially with low-dose therapy,

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

Table 25.1. Aspirin

Dose:	81-325 mg/day. Dose over 162 mg should be used for acute ischemia
Indications:	Primary prevention of myocardial infarction
	Secondary prevention of myocardial infarction
	Secondary prevention of stroke after TIA or stroke
	Acute therapy of myocardial infarction
	Acute therapy of unstable angina
	Prevention of saphenous vein bypass thrombosis
Toxicities:	GI upset
	Bleeding

and unless the patient has recently taken a dose the function of the transfused platelets should not be impaired. It has been reported that DDAVP will reverse aspirin inhibition and may be effective for emergency surgery in bleeding patients on aspirin therapy.

Aspirin/Warfarin Combination Therapy

There has been renewed interest in this combination for ischemic heart disease due to the theoretical advantage of both antiplatelet/antithrombotic effects of the combination. Early trials using warfarin at an INR of 1.5-2.0 and 60 mg/day of aspirin or INR of 3.0 - 4.5- with 100 mg/day of aspirin have shown therapeutic effectiveness with an acceptable small increase in bleeding. In the Turpie study examining patients with prosthetic valves, combined therapy resulted in lower incidence of both death and embolic phenomena. Bleeding was increased by 20% but this was outweighed by the benefits of this combination. Other provocative trials have shown the benefits of this combination in long-term therapy of patients with unstable angina, after myocardial infarction, and even in primary prevention in high-risk patients.

Currently it is recommended that 160 mg/day of aspirin be added to warfarin INR 2.5 - 3.5 for patients with prosthetic valves who have a thrombotic event or are otherwise at high risk for thrombosis. This would include, for example, patients with prosthetic mitral valves and atrial fibrillation. Although not supported by any trial data, it may be prudent to also treat these patients with proton pump inhibitors to help lessen the incidence of gastrointestinal bleeding.

Ticlopidine

Ticlopidine, a drug derived from thienopyridine, inhibits platelet aggregation at the newly discovered platelet receptor P_2Y_{12}. The antiplatelet effect appears to depend on a metabolite of the drug binding to the receptor. Functionally, ticlopidine appears to inhibit ADP-induced GP IIb/IIIa activation. The dose is 250 mg orally twice per day. It may takes up to seven days to achieve full antiplatelet effect, but this does lasts the life of the platelet. Ticlopidine has been shown to be effective in unstable angina, TIAs, stroke, and peripheral vascular disease. Unfortunately, due to its serious and potential fatal side-effects, the use of ticlopidine is rapidly declining.

Ticlopidine has several major side-effects including nausea (10%) and severe neutropenia (1%). The most worrisome side effect is the induction of thrombotic thrombocytopenic purpura in 1 of 1600 people that is fatal in 20-50% of cases. Patients with ticlopidine-induced TTP will often have symptoms that mimic neu-

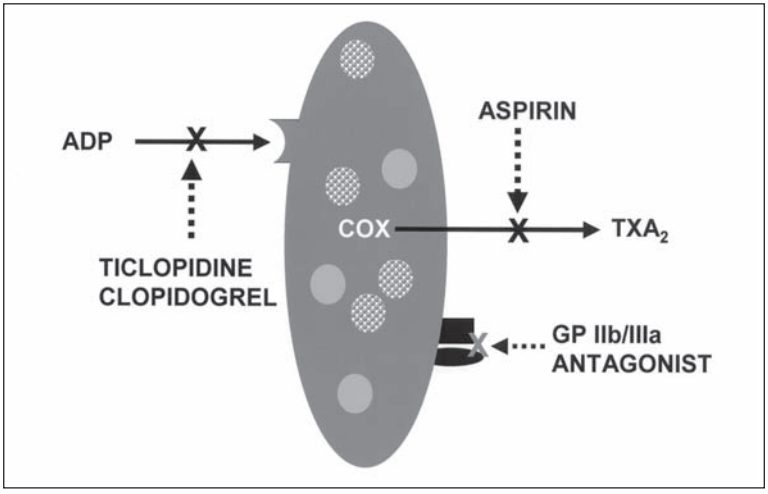

Fig. 25.1. Antiplatelet agents: mechanisms of Action.

rologic or cardiovascular disease. For example, a patient on ticlopidine for unstable angina may present with recurrent angina along with the other manifestations of TTP. The high incidence of TTP and neutropenia, along with the availability of a safer analog, has greatly limited the use of ticlopidine.

The incidence of bleeding with use of ticlopidine is equivalent to that of aspirin. Little data exists regarding specific therapy of bleeding complications, but in patients with life- threatening bleeding, consideration should be given to platelet transfusions.

Clopidogrel

Clopidogrel is also a thienopyridine that inhibits platelet ADP receptors. It is dosed as 75 mg orally once per day; a loading dose of 300-750 mg is being studied and seems to be effective in inducing a more rapid onset of antiplatelet action. Like ticlopidine, the antiplatelet effects can last for five days after cessation of therapy. In the CAPRIE trial, which has been the largest trial of clopidogrel to date, clopidogrel was slightly better than aspirin in the prevention of myocardial infarctions and strokes. The incidence of thrombocytopenia and neutropenia were not significantly different from that of aspirin.

Current indications for the use of clopidogrel are evolving. Patients who are intolerant of aspirin or who have failed aspirin should be considered for clopidogrel. There is increasing interest in combining aspirin and clopidogrel. The best studied use of this combination is after coronary stenting when one month of clopidogrel added to aspirin therapy reduced stent thrombosis. Recently the CURE trial demonstrated a 20% reduction in unfavorable outcomes when the combination of aspirin and clopidogrel was compared to aspirin alone in unstable angina. Aspirin/clopidogrel combination is now being studied in a variety of other disease states.

Table 25.2. Thienopyridines

Ticlopidine	
Dose:	250 mg po bid
Indications:	Secondary prevention of ischemic disease in patients intolerant of aspirin or aspirin failures
	Prevention of coronary stent thrombosis in combination with aspirin
Toxicities:	Gastrointestinal upset (10%)
	Neutropenia 1%
	Thrombotic thrombocytopenic purpura 1:1600
Clopidogrel	
Dose:	75 mg po once per day
Indications:	Secondary prevention of ischemic disease in patients intolerant of aspirin or aspirin failures
	Prevention of coronary stent thrombosis in combination with aspirin
Toxicities:	Gastrointestinal upset (10%)

Although it first appeared that, like ticlopidine, clopidogrel was also associated with the development of TTP, the incidence now appears to be much lower than that seen with ticlopidine and may not be above the baseline incidence of TTP.

Dipyridamole

Dipyridamole blocks degradation of cAMP, resulting in modest platelet inhibition. Due to lack of consistent effect in clinical trials, dipyridamole had fallen out of favor as an antiplatelet agent. Recently a trial using a novel sustained release form of dipyridamole and aspirin showed greater benefit in secondary stroke prevention than aspirin alone. However, the results of this isolated trial have been controversial due to problems with the size and conduct of the trial. Also in this trial the combination pill had no effect on cardiovascular events. Until further trial data is available from the ESPRIT trial, the role of dipyridamole in stroke prevention remains unclear. It should also be remembered that this trial utilized a special form of dipyridamole and that using the generic short-acting dipyridamole in combination with aspirin has been clearly demonstrated not to be effective.

Abciximab

Glycoprotein IIb/IIIa is a key platelet receptor that binds fibrinogen and von Willebrand protein to form the platelet aggregate. Activation of GP IIb/IIIa represents the "final common pathway" of platelet activation. No matter how the platelet is activated, the GP IIb/IIIa receptor must be activated for platelet aggregation to occur.

Abciximab is a novel antibody that blocks the GP IIb/IIIa and leads to profound suppression of platelet function. The antibody is a chimeric human-mouse antibody. Furthermore, its Fc portion is cleaved off so it can only bind and inhibit platelet functions but will not lead to splenic uptake and thrombocytopenia. Abciximab is administered in the dose of 0.25 mg/kg bolus then 0.125 μg/kg/min (maximum 10 mg/min) infusion for twelve hours. Abciximab needs to bind to more than 80% of the GP IIb/IIIa sites to impair platelet function. Soon after the infusion is ended, the antibody undergoes rapid redistribution and the antiplatelet effects wear off rapidly.

Table 25.3. Glycoprotien IIb/IIIa inhibitors

Abciximab
Dose: 0.25 mg/kg plus 0.125 μg/kg/min (maximum 10 mg/min) for twelve hours after PCI, along with
Heparin: 70 units/kg (maximum 7000 units) bolus with additional bolus to achieve an ACT of 200 seconds.

Tirofiban
Dose: 0.4 μg/kg/min for 30 minutes then an infusion of 0.1 μg/kg/min until resolution of the pain syndrome or for 12-24 hours after angiography
Give with aspirin and heparin

Eptifibatide
Dose:
Unstable angina: 180 μg/kg bolus followed by 2 μg/kg/min for up to 72 hours.
PCI: 135 μg/kg bolus prior to the procedure and then 0.5 μg/kg/min for 20-24 hours afterwards.
ESPRIT: 180 μg/kg bolus then 2 μg/kg/min for 18-24 hours. Second 180 μg/kg bolus ten minutes after the first.

Toxicities Common to All
Bleeding
Thrombocytopenia

Abciximab has been shown to be beneficial in patients undergoing cardiac percutaneous interventions (PCI) with and without stenting and in patients with refractory unstable angina before PCI. Use of abciximab has consistently reduced unfavorable outcomes by 30-50%. This initial benefit is sustained for at least three years. In the only "head-to-head" study of GP IIb/IIIa inhibitors abciximab was superior to tirofiban when used for PCI. Surprisingly, when used as a prolonged infusion as medical therapy (no planned PCI) for unstable angina, the use of abciximab did not improve outcome.

During PCI abciximab is given with heparin. Early studies showed an increased risk of bleeding with this combination. The EPILOG study demonstrated that the risk of bleeding with abciximab was greatly reduced using lower doses heparin without loss of effectiveness. Currently the recommended heparin dose is 70 units/kg (maximum 7000 units) bolus with additional boluses to achieve an ACT of 200 seconds. Excess bleeding was also prevented by early sheath removal (when ACT <175 sec).

Tirofiban

Tirofiban is the first of a large number of non-antibody GP IIb/IIIa inhibitors to be FDA- approved. Tirofiban is an intravenous synthetic non-peptide platelet antagonist. In trials with patients who suffered from unstable angina, tirofiban reduced myocardial infarctions and deaths by 22% at 30 days when used with heparin and aspirin in unstable angina patients. When used with PCI in patients presenting with unstable angina or myocardial infarction, tirofiban was effective but the beneficial effect dissipated after 30 days. As mentioned above, in a head-to-head comparison tirofiban was inferior to abciximab in PCI.

The dosing is weight-based with bolus of 0.4 μg/kg/min for 30 minutes and then an infusion of 0.1 μg/kg/min until resolution of the syndrome or for 12-24

hours after angiography. Patients with low creatinine clearances (<30 mL/min) should receive half the dose. Currently tirofiban's role is in the treatment of patients with unstable angina.

Eptifibatide

Eptifibatide is the second non-antibody anti GP IIb/IIIa agent to come on the market. A trend for better outcomes with eptifibatide was seen in patients undergoing PCI when compared to aspirin/heparin alone. In patients with unstable angina, 30-day outcomes were improved with the use of eptifibatide. The dose is 180 μg/kg bolus followed by 2 μg/kg/min for up to 72 hours. For patients undergoing PCI the original dose was 135 μg/kg bolus before the procedure and then 0.5 μg/kg/min for 20-24 hours afterwards. However, studies demonstrated that this dose was inadequate and resulted in a lesser degree of platelet inhibition than that seen in studies involving other GP IIb/IIIa blockers. A recent study (ESPRIT) using more aggressive dosing of eptifibatide showed better outcomes in PCI. Although this dosing is popular for patients undergoing PCI, eptifibatide has not been directly compared to abciximab.

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Further Use of GP IIb/IIIa Inhibitors

Intriguing pilot studies have shown that the use of GP IIb/IIIa inhibitors in combination with thrombolytic therapy improved the results and lowered dosage requirements of thrombolytic agents. For example, with the use of standard dose abciximab, only 50% of the dose of tPA is needed to achieve coronary patency equal or greater to that seen with standard dose tPA. Two large trials demonstrated that this approach reduced the rate of MI complications but had no effect on overall mortality. Studies are also underway combining GP IIb/IIIa inhibitors with low molecular weight heparins to attempt to improve outcomes in acute coronary syndromes. Early results indicate that there is no increase in bleeding seen with this combination.

GP IIb/IIIa Complications

The major side effect of these new agents is bleeding and thrombocytopenia. Bleeding is treated by giving platelet transfusions. This leads to redistribution of inhibitors and return of platelet function. In the EPIC trial no excess bleeding was seen in patients who had to undergo an emergency bypass, but other investigators have reported severe bleeding in these patients. It may be judicious to give a platelet transfusion before bypass or early in the operation in patients who have received GP IIa/IIIa inhibitors and need an emergency bypass if excessive bleeding is noted.

Severe thrombocytopenia has been reported in 0.5-2.0% of patients receiving IIb/IIIa inhibitors. The mechanism of thrombocytopenia is unknown but is speculated to be related to conformational changes in GP IIb/IIIa induced by binding of the inhibitors.

If a patient who has received a IIb/IIIa inhibitor presents with severe thrombocytopenia one should examine the blood smear to ensure that the low platelet count is not due to clumping of the platelets in the blood sample. If the patient has received heparin in the last three months one should also consider heparin-induced thrombocytopenia in the differential.

Experience with abciximab has shown that infusion of immune globulin or the use of steroids is not helpful. The inhibitors should be promptly stopped. Platelet transfusions result in a prompt rise in platelet count if severe thrombocytopenia is present.

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CHAPTER 26

Thrombolytic Therapy

The ability of tPA to cleave plasminogen to plasmin is far greater when plasminogen and tPA are both bound to the fibrin clot. Moreover, when plasmin is bound to fibrin, plasmin is protected from the action of circulating $alpha_2$-antiplasmin. In normal fibrinolysis, tPA binds to fibrin and then converts plasminogen to plasmin, which lyses the clot. Any excess tPA that escapes into the plasma is rapidly inactivated by plasminogen activator inhibitor-1 (PAI-1). Any plasmin which escapes into the plasma is rapidly snuffed out by $alpha_2$-antiplasmin. Thus, active fibrinolysis is confined to the thrombus itself.

In pharmacologic fibrinolysis, the excessive quantity of endogenous plasminogen activators overwhelms the inhibitors of fibrinolysis and leads to generalized fibrinolysis. Excess plasmin can destroy any thrombi and degrades circulating fibrinogen. Although tPA is more "clot specific" than streptokinase due to the presence of kringle regions that can bind fibrin, in practice the use of tPA has not resulted in less bleeding.

Agents

Streptokinase was the first thrombolytic agent. It is derived from *Streptococcus*. Streptokinase has a long half-life. Streptokinase first cleaves plasminogen by a cumbersome mechanism wherein streptokinase first binds to plasminogen. This complex then cleaves a new molecule of plasminogen to form plasmin. One unique side-effect is that patients can develop antibodies to streptokinase due to prior use or due to a recent Streptococcal infection.

tPA was one of the first drugs manufactured by recombinant DNA technology. Natural tPA is secreted by endothelial cells and is a direct activator of plasminogen. Currently tPA is made via recombinant DNA technology and costs 10 times as much as streptokinase. Interest has now shifted toward using genetically modified versions of tPA.

Urokinase (UK) is a direct activator of plasminogen. UK is not used for coronary disease but it is still popular for thrombolytic therapy at other sites, especially for catheter-based use. It is derived from human tissue culture media and recombinant derivatives are in development.

Anistreplase is a derivative of streptokinase. It is formed from the complex of streptokinase bound to plasminogen. The active site is blocked by an anisoyl group. In circulating blood this anisoyl group is released, resulting in an active molecule. The addition of anisoyl lengthens the half-life of native streptokinase from 23 minutes to 90 minutes. Like streptokinase, patients receiving anistreplase can develop antibodies to streptokinase due to prior use or recent Streptococcal infection. The treatment dose for myocardial infarction is 30 units intravenously.

Reteplase is a derivative of tPA. It is genetically engineered by expression of only one kringle region and the protease region of tPA. Like tPA, it is a direct plasminogen

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Table 26.1. Thrombolytic therapy

Streptokinase	
Myocardial infarction:	1.5 million units IV over one hour.
Urokinase	
Pulmonary embolism:	4400 units/kg over one minute load then 4400/kg/hour for 12 hours.
Arterial thrombosis:	4000 units/minute for four hours then 2000 units/minute for up to 44 hours
Tissue Plasminogen Activator	
Myocardial infarction:	15 mg/kg bolus, 0.75 mg/kg over 30 minutes, then 0.5 mg/kg over next hour.
Stroke:	0.9 mg/kg (maximum 90 mg) with ten percent of the dose given in one minute
Pulmonary embolism:	100 mg given over 2 hours
Anistreplase	
Myocardial infarction:	30 units IV over 5 minutes.
Reteplase	
Myocardial infarction:	two 10 unit boluses separated by 30 minutes.
Tenecteplase	
Myocardial infarction:	weight-based bolus over 5 seconds. <60 kg = 30 mg 60-69 kg = 35 mg 70-79 kg = 40 mg 80-89 kg = 45 mg >90 kg = 50 mg

activator. The drug is administered as two boluses of 10 units each. The second bolus is given 30 minutes after the first bolus. Each bolus is given over 2 minutes.

Reteplase (r-PA) is a derivative of tPA. It is genetically engineered by expression of only one kringle region and the protease region of tPA. Like tPA, it is a direct plasminogen activator. The drug is administered as two boluses of 10 units each. The second bolus is given 30 minutes after the first bolus. Each bolus is given over 2 minutes.

Tenecteplase (TNK-tPA) has three amino acid substations which produces a plasminogen activator with longer half-life and more resistant to PAI-1. It can be give as a single bolus which dramatically simplifies therapy.

Indications

Myocardial Infarction

Use of thrombolytic therapy in acute myocardial infarction has reduced the one month mortality rate by 18%. The effect is greatest if thrombolytic therapy is used early in the course of the myocardial infarction. In one trial mortality was reduced by 47% if thrombolytics were administered within 1 hour, 22.6% by 6 hours and 10% in 6 to 10 hours. Patients with anterior myocardial infarctions have markedly decreased mortality when treated with thrombolytic therapy. The elderly suffer the most from myocardial infarction and despite the risk in bleeding, have the most to gain by thrombolytic therapy. The greatest risk of these agents is serious bleeding. The risk of death due to hemorrhage is 1.1% vs 0.4% in controls, but the increased risk of bleeding is outweighed by the reduction in myocardial infarction-related

death. A patient who has had previous invasive procedures such as angiography is at risk for bleeding from arterial puncture sites. The choice of which agent to use remains controversial. Three trials showed identical results using streptokinase versus tPA, but the GUSTO trial that employed a different way to give tPA found a slight advantage in patients under 75 years of age treated within 6 hours of myocardial infarction. Recently the bolus dose agents have been more frequently used because of ease of administration.

The use of immediate angiography with stenting has been shown to offer improved outcomes when compared to thrombolytic therapy alone. However, if catheterization laboratories are not immediately available, the delay in care that results form waiting to transfer the patient must be weighed against the benefits of immediate thrombolytic therapy.

Stroke

Since most strokes are thrombotic in origin it is tempting to consider thrombolytic therapy, but the serious side-effect of intracranial bleeding has made researchers reluctant to consider this therapy. Recent studies have shown that, if tPA therapy is given within 3 hours of stroke onset, there is an improvement in outcome at 6 months. Currently one should consider thrombolytic therapy for patients with stroke if they are evaluated in the very early stages of a stroke and have no major risk factors for bleeding. This therapy remains impractical for the majority of stroke patients. Current research is being performed with catheter-based thrombolytic therapy.

Deep Venous Thrombosis/Pulmonary Embolism

Although it seems attractive, thrombolytic therapy for large clots in the leg or lung has not proven clinically effective in clinical trials. There is improvement in blood flow in some patients soon after thrombolytic therapy, but long-term clinical outcomes in deep venous thrombosis or pulmonary embolism are not improved. A recent trial using thrombolytic therapy for patients with right heart strain and pulmonary embolism did not demonstrate an advantage for lytic therapy for "hard" clinical endpoints such as mortality. Post-phlebitic syndrome has not been shown to be ameliorated with use of thrombolytic agents for DVT. Moreover, the risk of fatal bleeding is 1%/day of therapy. Thus, thrombolytic therapy for deep venous thrombosis/pulmonary embolism is usually not recommended except under unusual circumstances.

Complications

The major complication of thrombolytic therapy is bleeding. Patients bleed at sites of previous injury due to lysis of previously formed thrombus. Patients may also have bleeding due to underlying vascular problems. Patient who suffer intracranial hemorrhage with thrombolytic therapy often have underlying cerebrovascular amyloid.

Thrombolytic therapy affects every aspect of the hemostatic system. Patients will have a low fibrinogen, elevated PT and aPTT due to destruction of factors V and VIII. Platelet dysfunction will occur due to binding of fibrinogen fragments blocking platelet receptors and also cleaving platelet receptors. Finally, there will lysis of formed thrombi.

Patients who suffer severe bleeding after thrombolytic therapy should immediately have a PT-INR, aPTT, fibrinogen level and platelet count performed. Ten units of cryoprecipitate should be infused to replace fibrinogen and factor VIII. If the PT and aPTT remain elevated, two units of plasma should then be infused. If bleeding persists, platelets should be given. If the patient is having an intracranial hemorrhage, empiric therapy with cryoprecipitate, platelets and plasma should be given.

Although reversal of the fibrinolytic state can be achieved with the use of antifibrinolytic agents, this is rarely required. The fibrinolytic state, especially with tPA, is short-lived. Infusion of fibrinogen and plasma will shorten the duration of the fibrinolytic state. Finally, reversal of fibrinolysis may result in reformation of the culprit thrombus that would then be refractory to lysis.

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CHAPTER 27

Bleeding and Thrombosis in Cancer Patients

Cancer is a common disease; an estimated one in four people develops some form of cancer in a lifetime. Both excessive bleeding and thrombosis may be seen in cancer patients. These may be due to the direct effect of the malignant cell or to the byproducts of the cancer having a profound effect on the hemostatic system.

Bleeding Syndromes

Acute Promyelocytic Leukemia (APL)

The hemostatic defects in patients with APL are multiple. Most if not all patients with APL have evidence of DIC at the time of diagnosis. Patients with APL have a higher risk of death during induction therapy when compared with patients with other forms of leukemia. But, once is remission, APL patients have a higher cure rate than most patients with leukemia. APL is also unique among leukemias in that biological therapy with retinoic acid is effective in inducing remission.

Patients can present with pancytopenia due to leukemic marrow replacement or with diffuse bleeding due to DIC and thrombocytopenia. Life-threatening bleeding such as intracranial hemorrhage may occur at any time until the leukemia is put into remission.

Etiology

The etiology of the hemostatic defects in APL is complex and is thought to be the result of DIC, fibrinolysis, and the release of other procoagulant enzymes.

The leukemic cell contains tissue factor, which can directly activate coagulation. In the test tube, the APL cells may function as activators of coagulation and stimulate thrombin generation. Patients with APL have high levels of markers of DIC such as thrombin-antithrombin III complexes. However, patients with APL tend to have normal levels of antithrombin III, unlike patients with DIC due to other causes.

Patients with APL also show signs of increased fibrinolysis. The leukemic cells contain fibrinolytic enzymes such as urokinase. In addition, brisk fibrinolysis due to thrombin generation is also present. Inhibitors of fibrinolysis such as alpha$_2$-antiplasmin are reduced, sometimes markedly so.

APL cells, like their non-malignant counterparts, contain a number of proteases. Recently these proteases have been implicated in the coagulation defects of APL. These proteases can reduce von Willebrand factor and fibrinogen which further augments the coagulation defects. In addition, the proteases may disrupt vascular integrity, leading to bleeding.

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Table 27.1. Initial evaluation and management of patients with APL

1. Obtain baseline PT-INR, aPTT, platelet count, fibrinogen, D-dimer.
2. Based on laboratories, replace using following goals:
   - PT-INR < 2.0 and aPTT > 1.5 x normal: two units of fresh frozen plasma.
   - platelets under 50,000/μl: give one plateletpheresis unit or 6-8 platelet concentrates.
   - fibrinogen under 100 mg/dl: give 10 units of cryoprecipitate.
3. If coagulation defects are initially present, follow laboratory every six hours.
4. If patient required over 40 units of cryoprecipitate in 12 hours or has thrombosis, consider starting heparin at 500 units/hour.
5. If patient has severe fibrinolysis (alpha$_2$ antiplasmin under 40%), give antifibrinolytic therapy along with heparin.

Diagnosis

The diagnosis of APL can be straightforward when the leukemic cells are promyelocytes bulging with Auer rods. Some patients have the microgranular form without obvious Auer rods. Demonstrating the classic translocation via molecular means is now the gold standard. One can directly detect the 15:17 rearrangement by using fluorescent in-site hybridization. Upon diagnosis of APL, one should obtain a complete coagulation profile including PT, aPTT, fibrinogen, platelet count and D-Dimers. Change in fibrinogen levels tends to be a good marker of progress in treating the coagulation defects. Obtaining an alpha$_2$-antiplasmin level may help guide therapy in patients with severe defects.

Therapy

Therapy of APL involves treating both the leukemia and the coagulopathy.

Currently the standard treatment for APL is trans-retinoic acid (ATRA) in combination with chemotherapy. This will induce remission in over 90% of patients, and a sizable majority of these patients will be cured of their APL. ATRA therapy will also lead to early correction of the coagulation defects, often within the first week of therapy. This is in stark contrast to the chemotherapy era when the coagulation defects would become worse with therapy. Rare reports of massive thrombosis complicating therapy with ATRA exist, but the relationship to either the APL or ATRA is unknown.

Therapy for the coagulation defects consists of aggressive transfusion therapy support and possible use of other pharmacologic agents to control the DIC (Table 27.1). Patients should receive frequent laboratory monitoring, up to every six hours, so the effectiveness of the transfusion therapy can be seen and further therapy given. One should try to maintain the fibrinogen level at over 100mg/dl and the platelet count at over 50,000/uL. Some patients may require over 100 units of cryoprecipitate a day to achieve a stable fibrinogen level.

Controversy still exists over the role of heparin in therapy of APL. Although attractive for its ability to quench thrombin, heparin use can lead to profound bleeding. One should consider the use of heparin in certain circumstances. Patients who require large amounts of cryoprecipitate (> 40 units/day) or other clotting factors and have poor recovery should be considered for heparin therapy. The rare patient who has thrombosis should also receive heparin. One should start with a low dose of 500 units/hr without bolus and monitor with heparin levels. Aggressive factor replacement should be used along with the heparin.

Rarely, other agents such as antifibrinolytic agents can be considered. Patients who have primarily a fibrinolytic presentation can be identified by observing an alpha$_2$-antiplasmin level of under 40%. In these patients one should use antifibrinolytic agents such as aminocaproic or tranexamic acid. These should be given with heparin to prevent thrombosis.

Other Leukemias and Myelodysplastic Syndromes

Along with the obvious thrombocytopenia due to marrow replacement, other coagulation defects may be seen in leukemias. DIC can be seen in other forms of acute leukemia apart from APL. DIC is frequently seen in acute monocytic leukemia. Patients with acute lymphocytic leukemia may also have DIC; one report showed that most patients develop signs of DIC with induction therapy.

The most common coagulation defect in ALL is associated with the use of L-asparaginase. Both bleeding and thrombotic complications have been reported with the use of this effective chemotherapeutic agent. L-asparaginase decreases hepatic synthesis of many proteins, including coagulation factors. Despite very low fibrinogen and markedly prolonged clotting times, bleeding is rarely seen. Paradoxically, thrombosis is seen in 0.5-4% of patients treated with L-asparaginase. Strokes due to venous sinus or arterial thrombosis may be seen, as well as deep venous thrombosis and pulmonary embolism. Levels of the natural anticoagulants such as protein S and antithrombin III are reduced with L-asparaginase and this may contribute to the hypercoagulable state. Patients with thrombosis should receive factor replacement and heparin.

Multiple defects are found in the platelets of patients with myelodysplastic syndrome. These include reduced platelet aggregation in response to a variety of agonists, decreased platelet stores of von Willebrand protein and fibrinogen. These patients may have severe bleeding even with platelet counts above 50,000/μL. Therapy of bleeding in myelodysplasia is often unsatisfactory with some patients not responding even to platelet transfusions.

Myeloproliferative Syndromes

A higher incidence of bleeding is seen in many of the myeloproliferative syndromes, but the bleeding rarely results in major morbidity. One-quarter of patients with polycythemia vera experience some bleeding but this is very rarely the cause of death. Most series report that 30% of patients with essential thrombocytosis have bleeding. Paradoxically, the risk of bleeding appears to increase with platelet counts above one million. Some patients with extreme thrombocytosis have evidence of acquired von Willebrand disease. Most bleeding in myeloproliferative syndromes consists of mucocutaneous bleeding or bruising with only a few reports of major bleeding. The use of drugs that inhibit platelet function is associated with a higher incidence of bleeding.

Despite the large number of reported in-vitro abnormalities, there is no one specific platelet defect that appears to explain or predict bleeding in patients with myeloproliferative syndromes.

Therapy is non-specific. Some patients with markedly elevated platelet counts will respond to lowering the counts to below 1,000,000/μl. This can be done rapidly by plateletpheresis or slowly (over days) by chemotherapy. Rare patients will have persistent oozing and bleeding after major procedures. Frequent platelet transfusions may be of value in these patients along with antifibrinolytic therapy.

Table 27.2. Coagulation defects associated with paraproteins

1. Monoclonal antibodies inhibiting coagulation factors
2. Monoclonal antibodies inhibiting platelet receptors
3. Monoclonal antibodies inhibiting fibrin formation
4. Amyloid deposits adsorbing factor X
5. Amyloid deposits adsorbing $alpha_2$ antiplasmin

Dysproteinemias

Dysproteinemia, the abnormal production of immunoglobulin, can affect many steps of the coagulation system and lead to severe bleeding. Multiple coagulation abnormalities have been described in patients with dysproteinemias (Table 27.2).

First, the physical structure of the fibrin clot may be abnormal due to increased serum globulins. Polymerization of fibrin is impaired in some patients with circulating light chains, which is suggested by prolonged thrombin or reptilase times. Myeloma proteins have also been shown to inhibit the thrombin time in normal plasma. The site for factor XIII activity on fibrin strands can be blocked by an abnormal protein.

Platelet abnormalities are less well defined in patients with myeloma although prolonged bleeding times have been described. Presumably both defects are due to inhibition of platelet function by abnormal proteins.

The abnormal protein can bind to coagulation factors leading to inhibition of factor function, especially of factor VIII. Monoclonal proteins with specificity toward platelet GP IIb/IIIa have been reported. These patients may have mild to no thrombocytopenia but have a very severe bleeding diathesis.

Therapy for the hemostatic defects in the dysproteinemic syndromes includes removal of the offending protein, either by reducing synthesis through treating the plasma cell dyscrasia or by intensive plasmapheresis. In several patients, return of normal hemostasis was correlated with a substantial reduction in the paraprotein spike in the serum.

Patients with systemic amyloidosis, either primary or that associated with myeloma, often demonstrate a marked increase in easy bruisability and other bleeding symptoms. The most common defects in coagulation testing of patients with amyloid is an elevation in the thrombin time which is seen in 30-80% of cases. An increased prothrombin time is seen in 20-24% of cases and an increased aPTT in up to 70%.

Factor X deficiency was first reported to be associated with amyloidosis in 1962; subsequent studies have shown that the clotting factor is adsorbed onto amyloid proteins. Splenectomy, plasmapheresis, and treatment with melphalan and prednisone have been reported to reduce the amyloid burden and to increase the factor X levels. In patients with factor X deficiency receiving bone marrow transplant, improvement in factor X levels was seen in those patients who responded to the transplant.

Another cause of bleeding in patients with systemic amyloidosis is systemic fibrino(geno)lysis. The euglobulin clot lysis time is shortened with striking decreases in $Alpha_2$-PI, plasminogen, and circulating plasmin-antiplasmin complexes. Some patients have also been reported to have elevated plasma levels of tissue-type plasminogen activator. The mechanisms responsible for the fibrinolytic state are not known

but hypotheses include increased release of plasminogen activators, decreased plasminogen activator inhibitors, blood vessels infiltrated with amyloid, decreased $_2$-PI because of its adsorption onto amyloid fibrils, or perhaps amyloid liver disease. The use of fibrinolytic inhibitors such as EACA or tranexamic acid has both corrected laboratory tests of fibrinolysis and reduced bleeding symptoms.

Cancer and Thrombosis

Thrombosis As a Paraneoplastic Syndrome

Thrombosis can be the presenting sign of cancer. As many as 10-20% of older patients who present with a deep venous thrombosis will be found to have cancer on initial evaluation. Furthermore, over the next two years as many of 25% of patients will develop cancer. Certain signs are more worrisome for cancer as an underlying cause of the thrombosis. Patients with warfarin-refractory thrombosis, idiopathic bilateral deep vein thrombosis, or both arterial and venous thrombosis seem to be at particular risk for having an underlying malignancy.

Rare patients can present with thrombosis and associated disseminated intravascular coagulation. Patients with tumor-related DIC have thrombosis with low platelets and an abnormal coagulation profile. These patients may also develop non-bacterial thrombotic endocarditis and have multiple embolic events.

The cancers most frequently associated with thrombosis are adenocarcinoma of the lung and gastrointestinal cancers, especially pancreatic adenocarcinoma. Primary brain tumors are also associated with a higher risk of thrombosis.

The etiology of the thrombosis may be direct activation of factor VII by tumor-expressed tissue factor. A direct activator of factor X has also been implicated. Patients with cancer have elevations of inflammatory cytokines that can further augment the hypercoagulable state. Chemotherapy can also increase the risk of thrombosis perhaps due to endothelial damage. Finally, the use of tamoxifen is associated with an increased risk of thrombosis.

Cancer-related thrombosis requires anticoagulation. Initial therapy of thrombosis should be with low molecular weight heparin. Evidence from clinical trials suggests that cancer patients have improved outcomes, including decreased mortality, when LMWH is used as first-line therapy. Recently several trials have demonstrated that long term use of LMWH instead of warfarin therapy significantly reduced the recurrence of thrombosis. Strong consideration should be given to the long-term use of LMWH in patients with "thrombogenic" tumors such as pancreatic cancer, gastric cancer, adenocarcinoma of the lung, and primary brain tumors.

A few cancer patients are refractory to warfarin. However, most patients will not fail warfarin and this is a reasonable choice for initial therapy in most patients except for those with evidence of DIC or those with pancreatic tumors who should be treated with long-term heparin. Patients who have failed warfarin also need to be treated with heparin. Brain tumors or brain metastases are not a contraindication to warfarin. It should be remembered that placement of an inferior vena cava filter without concurrent anticoagulation is associated with an unacceptable rate of complications, including death from massive thrombosis.

Myeloproliferative Syndromes

Thrombosis is the most common cause of death in the myeloproliferative syndromes. Although many patients will have markedly elevated blood counts, patients with essential thrombocytosis may have thrombotic complications when the platelet

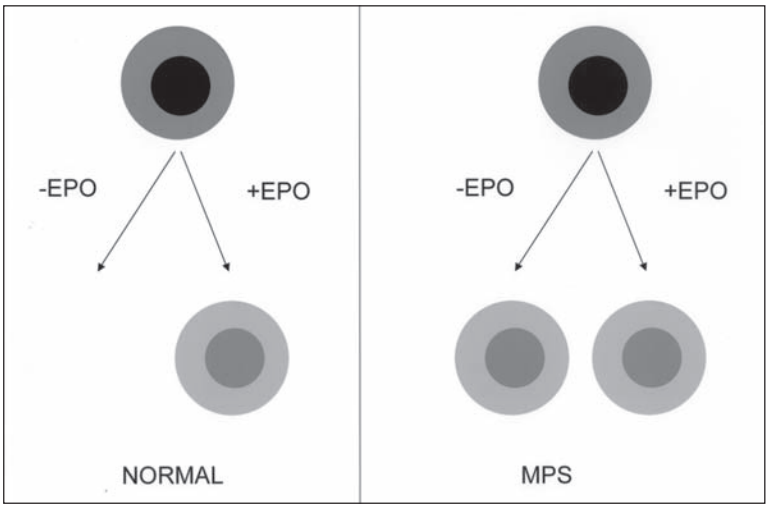

Fig. 27.1. Endogenous erythoid colony assay.

count is in the 4-600,000/μL range. Patients with polycythemia rubra vera are also at increased risk of thrombosis when their hematocrits are over 55%. The thrombosis may be due to small vessel events, perhaps in part from increased viscosity, or large vessel thrombosis. Patients with myeloproliferative syndromes have a higher risk of thrombosis even with relatively normal blood counts, suggesting an intrinsic defect in the blood cells leading to thrombosis.

Patients with myeloproliferative syndromes may have thrombosis in any location, but thromboses at two certain sites should raise concern about an underlying myeloproliferative syndrome. Patients with Budd-Chiari and other visceral vein thromboses have a high incidence of underlying myeloproliferative syndromes. Patients with essential thrombocytosis can also have platelet occlusion of the small digital vessels leading to erthryomelalgia. These patients will have swollen, red and very painful digits. The patients may only have slightly elevated platelet counts and are often misdiagnosed with arthritis. One helpful diagnostic clue is that these patients will respond dramatically to a single aspirin per day.

Certain patients, especially those with Budd-Chiari syndrome, may have an "occult" myeloproliferative syndrome. Although there may be no evidence of any hematological disorder on the peripheral smear or bone marrow aspirate, an established clonal proliferation of abnormal hematopoietic cells is present. A sensitive test for myeloproliferative disorders is the endogenous erythroid colony assay. This test depends on the ability of the abnormal clone to grow in culture without erythropoietin. A positive test can predate the onset of an overt myeloproliferative disorder by months to years. Up to 25-50% of patients with "idiopathic" Budd-Chiari syndrome will have a myeloproliferative disorder diagnosed by erythroid colony assay.

The diagnosis of a myeloproliferative syndrome is easy in patients with very abnormal blood counts. However, many patients will have only mildly elevated blood counts or normal counts. In these patients the endogenous erythroid colony assay is

particularly useful in diagnosis. Although bone marrow biopsies are frequently done, they often lack specificity to diagnose myeloproliferative syndromes unless accompanied by genetic studies.

Therapy of Thrombosis in Myeloproliferative Syndromes

Intravenous heparin followed by warfarin is indicated for most patients with acute venous thromboembolism complicating the myeloproliferative disorders. Catheter-based thrombolytic therapy should be considered in patients who have acute occlusion of the hepatic or portal veins. Long-term oral anticoagulants (INR 2-3) are usually recommended for prevention of recurrent thromboses. In a few instances, liver transplantation has been successful in treating liver failure due to Budd-Chiari syndrome.

Antiplatelet therapy, usually with aspirin, is recommended for treatment of patients with cerebral, coronary artery, or peripheral vascular thrombosis. Low doses of aspirin (80-360 mg/d) are preferable in patients with myeloproliferative disease because the risk of bleeding with aspirin is dose-related. One study showed an aspirin dose of 100 mg/day appeared to be effective for preventing thrombosis without excessive bleeding as long as the platelet count was kept at under 1,000,000/μl. There is currently no data concerning the use of newer agents such as clopidogrel. A few patients will develop serious recurrent thromboembolic events despite treatment with aspirin. In such cases, combined anticoagulation (INR 2-3) and antiplatelet therapy should be considered.

In addition to antithrombotic therapy, treating high platelet counts should be considered in patients with myeloproliferative disorders and a history of thrombosis. Hydroxyurea (1 gm daily to start) is the preferred therapy. A randomized trial in high-risk patients (age over 60 or history of thrombosis) demonstrated that use of hydroxyurea to maintain the platelet count at less than 600,000 ul/ml was associated with significantly less thrombosis (3.6% with hydroxyurea vs 24% controls). A platelet count of 250-450,000/μl is an appropriate target.

Increasingly, anagrelide is being used to lower platelet counts in patients with myeloproliferative syndromes. Unlike with hydroxyurea, no clinical trial data exists regarding the efficacy of anagrelide preventing thrombosis in high-risk patients. In fact, one long-term study of patients even demonstrated a 20% thrombosis rate with its use. Anagrelide has also been associated with cardiovascular side effects and is not recommended for patients with a history of heart disease.

An even more difficult problem is whether to reduce platelet counts or to give aspirin to patients with myeloproliferative disorders who do not have a history of thrombosis. Platelet reduction with hydroxyurea should be considered in asymptomatic older subjects with platelet counts over 1,000,000/μl, particularly if they have atherosclerosis, risk factors for arterial disease, or symptoms of vascular ischemia. Also important is controlling reversible risk factors such as smoking or elevated cholesterol.

Aspirin therapy had been feared in myeloproliferative syndromes due to concerns about bleeding. High rates of bleeding were seen in early studies using large doses of aspirin. However, a recent study using low dose aspirin (100mg) in patients with polycythemia demonstrated a significant reduction in thrombosis events without an increase risk of major bleeds. Aspirin therapy should be strongly considered in patients with myeloproliferative syndromes who do not show signs of clinical bleeding. Patients with pre-existing vascular disease or risk factors should be on aspirin therapy unless there is a major contraindication.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH remains a poorly understood clonal hematopoietic disorder. One of the leading causes of morbidity and mortality in patients with PNH is thrombosis. Patients can present with venous or arterial thrombosis. Also, like myeloproliferative syndromes, PNH is associated with a high incidence of visceral vein thrombosis. The cause of the hypercoagulable state is unknown, but complement-activated platelets have been implicated. In two large series, the rate of thrombosis in PNH was 28-39% with thrombosis leading to death in 58%. Given the high rate of thrombosis, it has been suggested that patients with PNH should receive prophylactic anticoagulation, even without a history of thrombosis. Patients with thrombosis should be aggressively treated but breakthrough thrombosis has been reported, even in patients on heparin.

Catheter Thrombosis

Central venous catheters are essential to many aspects of cancer therapy. The clinically apparent thrombosis incidence for catheters is estimated to be 5-30%. The signs of catheter thrombosis are non-specific and the incidence of thrombosis is thought to be underestimated. Central venous catheters are often coated with sheaths of fibrin soon after introduction. Pulmonary artery catheters directly visualized at surgery 1-2 hours after insertion were all found to be coated with thrombus. Catheter thrombosis can also be a sign of HIT since heparin is often used to ensure patency.

Therapy is not well defined. Intuitively, removing the catheter will remove the nidus of thrombus and if possible this should be done. If the patient is stable one should consider anticoagulation for 4-6 weeks. Given the low risk of long-term sequellae, there is little indication for thrombolytic therapy.

Prevention of catheter thrombosis is difficult. Trials with long-term tunneled catheters have shown variable effectiveness of one milligrams of warfarin per day in preventing thrombosis. However, in patients sick with cancer this small amount of warfarin may induce anticoagulation and monitoring of the INR should be considered.

Chemotherapeutic Agents

Adjuvant chemotherapy for breast cancer has been associated with an increased risk of both arterial and venous thromboembolism (in 5-7% of patients). The thrombogenic stimulus is not clear, but this could reflect vascular damage by the chemotherapeutic agents, or perhaps a reduction in protein C or protein S concentrations. One trial has shown that low levels of warfarin (INR 1.5) can prevent the thrombotic events.

Patients receiving certain chemotherapeutic agents can develop a severe thrombotic microangiopathy closely resembling the hemolytic-uremic syndrome. Mitomycin C is most commonly associated with this disorder, but other agents include Cis-platinum, Daunorubicin, Cytosine Arabinoside, Bleomycin, cyclosporine, and FK506. Unusually large multimers of von Willebrand factor have been demonstrated in the plasma. The disorder is usually fulminant and rapidly fatal, but anecdotal reports of successful treatment with staphylococcal protein A columns have been published. An unusual aspect of mitomycin C-induced microangiopathy is clinical worsening after patients are transfused with red blood cells.

Bone Marrow Transplantation

Hepatic veno-occlusive disease (VOD) is a relatively common complication of bone marrow transplantation and is seen in 1-50% of patients, but the frequency seems to vary widely from center to center. The clinical syndrome includes weight gain, hepatic tenderness and jaundice soon after transplantation which can progress to liver failure and the hepatorenal syndrome. In one large study of 355 patients, hepatic VOD developed in 54% with a mortality rate of 39% in severe cases. Early thrombosis of the hepatic venules leading to obstruction and eventual fibrosis is the most commonly accepted mechanism for VOD. Pre-existing liver dysfunction, especially hepatitis C, is an important risk factor for development of the disorder. Conditioning regimens that include busulfan also increase the incidence. The risk also appears to be higher in patients undergoing allogeneic rather than autologous transplantation.

Multiple coagulation defects have been demonstrated, but low levels of protein C prior to transplant were a strong and reproducible predictor of VOD. For example, all patients with a baseline protein C value of less than 66% of normal developed the syndrome. At present, it is unclear whether the lower level of protein C is simply a surrogate marker for underlying liver disease, or it constitutes a specific pathogenetic mechanism. Elevated levels of plasminogen activator inhibitor-1 have been suggested as a non-invasive test for VOD.

Prothrombotic cytokines such as TNF and IL-6 have been shown to be elevated in patients with VOD, and markers of activation of hemostasis such as F1.2 and TAT are also increased. Antithrombotic therapy has been employed to halt the thrombotic process. A recent randomized trial demonstrated that heparin at a dose of 100 U/kg/day beginning eight days prior to transplant and continuing for 30 days thereafter decreased the rate of VOD from 13 to 2.5% in patients with autologous transplants. The incidence of VOD using this heparin therapy in patients receiving allogeneic transplants fell from 18 to 0%. Thrombolytic therapy with urokinase or t-PA has been used for treatment of patients with established VOD. A small pilot study of 7 patients with severe VOD treated with 10 mg/d of t-PA for two days followed by heparin showed a response in 5 of 7 patients, but a larger follow-up study demonstrated a high risk of bleeding, especially in patients who already had developed multi-organ system failure. Early reports also indicate that defibrotide is effective in therapy of VOD. Currently a large trial of this agent is underway to determine its usefulness in VOD.

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CHAPTER 28

Bleeding and Thrombosis in Pregnancy

Thrombocytopenia

Up to 2% of pregnant women will develop platelet counts of under 100,000/μL during pregnancy (Table 28.1). The most common cause is termed "gestational thrombocytopenia." This is an exaggeration of the low normal platelet count seen in pregnant women. Counts are usually above 75,000/μL but may fall as low as 50,000/μL at the time of delivery. No therapy is required as the fetus is not affected and the mother does not have an increased risk of bleeding. Diagnosis is by history and by following the trend of the platelet count.

Pregnancy complications such as HELLP syndrome and thrombotic microangiopathies also present with low platelet counts, but these can be diagnosed by history and clinical presentation.

Women with ITP can either develop the disease during pregnancy or have a worsening of the symptoms when pregnant. Platelet counts often dramatically drop during the first trimester in women with ITP. Early management is conservative with low doses of prednisone (20-40 mg/day) to keep the count above 30,000/μL (Table 28.2). Immunoglobulin in the dose of 1g/kg for two days is also effective but there are case reports of pulmonary edema when immunoglobulin is given late in pregnancy. Rarely patients who are refractory to immune globulin and prednisone will require splenectomy which can be performed during the second trimester.

Most controversy centers around management of the delivery. In the past it was feared that fetal thrombocytopenia could lead to intracranial hemorrhage; therefore, caesarean section was always recommended. It now appears that most cases of intracranial hemorrhage are due to alloimmune thrombocytopenia and not ITP. Furthermore, in a mother who has ITP, the nadir of the child's platelet count occurs not at birth but several days later.

Attempts have been made to measure the fetal platelet count before birth using either percutaneous umbilical blood sampling (PUBS) or scalp platelet counts. Neither of these approaches is without hazard. PUBS may result in bleeding and the

Table 28.1. Causes of pregnancy-related thrombocytopenia

- Drug-related thrombocytopenia
- Gestational thrombocytopenia
- HELLP syndrome
- HIV disease
- Immune thrombocytopenia
- Thrombotic microangiopathies
- Type 2b von Willebrand disease

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

Table 28.2. Therapy of ITP in pregnancy

- Prednisone 20-40 mg/day to achieve platelet count over 30,000/μl
- Immune globulin 1 gram/kg repeated in 24 hours or anti-D 75 ub/kg in the 2nd or 3rd trimester
- Consider splenectomy in second trimester if ITP is refractory

loss of the child or the need for emergency delivery. Furthermore, if the PUBS is performed several days before delivery, the child's platelet count may be different by the time of delivery. Obtaining fetal scalp platelet counts is technically demanding and the counts are prone to underestimation. Most women with ITP are being managed with vaginal delivery given the very low risk of intracranial hemorrhage.

Von Willebrand Disease

Levels of von Willebrand protein increase dramatically with pregnancy. The vast majority of patients with Type 1 von Willebrand disease will normalize their levels with pregnancy and will not require any therapy for delivery. One should obtain a von Willebrand panel at 32 weeks to ensure normal levels. Types other than 1 may require therapy at delivery. It is desirable to avoid DDAVP or factor replacement until after the cord is clamped. Patients with severe non-type 1 von Willebrand disease may have severe postpartum bleeding and should receive aggressive therapy after delivery. Patients with type 2b von Willebrand disease may have mild to moderate thrombocytopenia. This is due to the increased production of the abnormal von Willebrand factor that can bind to platelets.

Other Bleeding Disorders

Women who suffer from rare bleeding disorders require plasma or platelet infusions at the time of delivery and for several days afterward until postpartum bleeding stops. Specific details should follow the recommendations in Chapter 6. In patients with severe bleeding disorders the incidence of miscarriages appears to be increased, perhaps due to placental separation due to hemorrhage.

Pregnancy-Related Thrombotic Microangiopathies

Pregnancy-Related TTP

TTP can occur anytime during pregnancy. Diagnostic confusion is often present due to the overlap of TTP and HELLP syndrome. A unique presentation of TTP may occur in the second trimester at 20-22 weeks. The fetus is uninvolved with no evidence of infarction or thrombocytopenia if the mother survives. The pregnancy somehow promotes TTP since the TTP will resolve with termination and can recur with the next pregnancy. Therapy is either termination of pregnancy or attempting to support the patient with plasma exchange until delivery. Many patients will have relapse with future pregnancies so this information must be weighed in planning future pregnancies.

HELLP Syndrome

The acronym HELLP (**H**emolysis, **E**levated **L**iver function tests, **L**ow **P**latelets) syndrome describes a variant of pre-eclampsia. Classically, HELLP syndrome occurs after 28 weeks in a patient suffering from pre-eclampsia. The pre-eclampsia need

not be severe. The first sign is a drop in the platelet count followed by elevated liver function tests such as the AST. Schistocytes are abundant on the peripheral smear. HELLP can progress to liver failure and deaths are reported due to hepatic rupture. Unlike TTP, fetal involvement is present in HELLP syndrome with fetal thrombocytopenia reported in 30% of cases. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will often result in cessation of the TTP, but refractory cases will require plasma exchange. A variant of HELLP syndrome is seen in patients with antiphospholipid antibody disease who may present at 20-24 weeks with HELLP. These patients may have heparin-refractory thrombosis and require delivery to stop the HELLP.

Post-partum Hemolytic Uremic Syndrome

An unusual complication of pregnancy is an HUS-type syndrome seen up to 28 weeks postpartum. This form of HUS is severe and permanent renal failure often results despite aggressive therapy.

Estrogen, Pregnancy, and Venous Thromboembolic Disease

Oral Contraceptives and Thrombosis

Since their introduction several decades ago, oral contraceptive pills (OCP) have been found to increase the risk of thrombosis. Currently the relative risk of thrombosis for those on OCP is increased about three-fold. However, given that the baseline risk of thrombosis in a young women is only about 3:10,000, the use of OCP leads to one extra thrombosis per 1666 women. Presence of factor V Leiden increases the relative risk 33-fold which translates to a risk of one thrombosis for every 333 women treated with OCP. Screening for factor V Leiden before starting OCP would deny many woman effective contraception. There also appears to be an increased risk of thrombosis for women on OCP with the prothrombin gene mutation.

Women who have had a previous thrombosis and are not currently anticoagulated should not use estrogen-containing OCP. Although the data is scant, it appears that the progesterone-only pill is not associated with an increased risk of thrombosis and is an option for these patients. It does appear that estrogen-containing OCP are a reasonable option for women who are already anticoagulated. Any slight increase in risk of thrombosis is outweighed by the advantage of preventing an unplanned pregnancy. The use of OCP in a patient known to be factor V Leiden positive but without a history of thrombosis is controversial. Although the risk is probably low, most would recommend against it unless the need for OCP was compelling.

Hormone Replacement Therapy and Thrombosis

It is now clear that HRT also leads to a three-fold higher risk of thrombosis. However, since the baseline risk of DVT in older women is higher (~1-2:1000), the absolute increase in risk is also higher. As with OCP, the risk is elevated in woman who are carriers of factor V Leiden, with the relative risk as high as 14 fold. In women with a past history of DVT, the risk of new DVT when on HRT is 10%/year. Therefore, unless anticoagulated, women with a history of DVT should not take HRT. Recent evidence also suggests that HRT increases the risk of stroke and myocardial infarction in all women.

Why Does Estrogen Cause Thrombosis?

There are many changes in the hemostatic system with the use of estrogen that "shift" women towards a hypercoagulable state. Levels of procoagulant proteins such as factors VII and VIII and fibrinogen increase. Of more importance are the decrements in the natural anticoagulants to levels commonly associated with thrombosis. Lower levels of antithrombin III and protein S are common. These natural changes are synergistic with any underlying hypercoagulable states. Up to 60% of women who develop thrombosis while pregnant will be found to have factor V Leiden. Women with factor V Leiden are more likely to have thrombosis with any estrogen exposure. Since estrogens raise the level of factor VIII, women may be more dependent on protein C to degrade factor V and control hemostasis. If the ability to degrade factor V is impaired, this may promote a hypercoagulable state.

Pregnancy and Thrombosis

Incidence

Deep venous thrombosis and its sequella, pulmonary embolism, are the most common causes of maternal death. The incidence of DVT/PE during pregnancy is 1 - 5/1,000 pregnancies (includes postpartum period). In women with previous deep venous thrombosis, the risk of recurrent thrombosis is 5 - 15%; this goes up to 60-75% in women with antithrombin III deficiency.

Diagnostic Investigation

Although the basic diagnostic approach to thromboembolism is the same in pregnant and non-pregnant women, concern about radiation exposure and the normal anatomical changes seen in pregnant women add complexity to the diagnostic algorithm.

Levels of **D-dimers** below a certain level (often 500 μg/ml) effectively rule out DVT/PE. In outpatient series, up to 30% of patients had low D-dimers which greatly simplified their work-up. D-dimer levels increase during normal pregnancy thus greatly reducing the utility of this test. Unfortunately, levels of D-dimers rise in normal pregnancy so by the third trimester most women will have "elevated" levels of D-dimers; this greatly reduces the utility of this test.

Leg studies for PE—One way to avoid radiation exposure in the setting of pregnancy is to perform non-invasive leg studies. This is prudent even in cases of a suspected pulmonary embolism since deep venous thrombosis will be present in 30-70% of women with proven pulmonary embolism. If deep venous thrombosis is present, this establishes the need for anticoagulant therapy and negates the need for further studies.

Duplex ultrasound has over 93% sensitivity and 98% specificity for proximal deep venous thrombosis even in late pregnancy. Duplex has a lower sensitivity (60%) to calf deep venous thrombosis. In case of a negative study one needs to do follow-up duplex to rule out clot extension.

Venogram has been considered in the past the "Gold Standard" of diagnosis of DVT but is rarely performed nowadays. The abdomen must be shielded in pregnancy which can lead to inadequate studies.

Table 28.3. Estimated fetal exposure

Procedure	Fetal Radiation (mrads)
Chest xray	50
Bilateral venography w/o abdomen shield	610
Unilateral venography w/o abdomen shield	305
Limited venography	< 50
Pulmonary angio via femoral route	405
Pulmonary angio via brachial route	6 - 18
Perfusion lung scan	18
Ventilation lung scan	3 - 20
Radionuclide venography	205
CT scan	< 16

V/Q scans are sensitive but not specific. V/Q scans are best viewed as "high probability","negative" and "non-diagnostic". One can minimize the radiation exposure by performing the perfusion scan first. If this is normal then there is no need to perform a ventilation scan.

CT scans are now the most popular method of diagnosing PE. Although specific, CT scans are only about 70-80--% sensitive and by themselves are not sufficient to rule out DVT.

Pulmonary angiogram is still the gold standard for diagnosis of a pulmonary embolism. In pregnant women the angiogram can be performed through the brachial artery which minimizes radiation to the abdomen.

In summary, a reasonable approach for a pregnant woman with a suspected DVT would be to perform a doppler on her legs. If this is negative but symptoms persist the doppler should be repeated the next day and one week later. In a woman with a suspected PE, leg studies should be performed first. If this is negative, then either CT or a V/Q scan should be performed. If either of these is negative and the woman is stable, the leg studies should be repeated one week later. If the patient is very symptomatic then pulmonary angiogram should be performed.

Estimated Fetal Radiation Exposure

Fetal exposure to radiation is a significant concern when evaluating the pregnant patient for venous thrombosis/pulmonary embolism (Table 28.3). Exposure of the fetus to less than 5,000 mrads is not teratogenic (threshold is in the range of 25,000 mrads). Threshold for oncogenicity is more controversial without definite studies. Review of the pertinent literature reveals it is likely that fetal exposure to small amounts (<5,000 mrads) may be associated with a relative risk of leukemogenesis of 1.3 - 1.8. This risk is far outweighed by the need for accurate diagnosis of deep venous thrombosis/pulmonary embolism.

Therapy of Deep Venous Thrombosis (Table 28.4)

Many studies have shown that LMWH is both safe and effective during pregnancy. Initial dosing is the same (i.e., enoxaparin 1 mg/kg every 12 hours). Patients with thrombosis will be on LMW heparin for the duration of the pregnancy, so levels should be followed with a therapeutic goal of 0.7-1.1 anti-Xa units 4 hours after injection. Use of warfarin at any time during the pregnancy is associated with increased risk of fetal malformation (especially from 6-12 weeks) and is best avoided.

Table 28.4. Therapy of deep venous thrombosis in pregnancy

- **Enoxaparin** 1 mg/kg every 12 hours to achieve levels of 0.7-1.2 anti-Xa units four hours after injection, or
- **Dalteparin** 100 units every 12 hours to achieve levels 0.7-1.2 anti-Xa units four hours after injection.

- Hold dose before delivery.
- Resume after delivery and start warfarin with 10 mg loading dose.
- Continue warfarin for minimum of 6 months of antithrombotic therapy (heparin plus warfarin) which must be extended to include 6 weeks post-partum period in women with thrombosis early in pregnancy.

Standard heparin has an increased risk of osteoporosis (up to 30%) and if used must be monitored with heparin levels as the aPTT is an unreliable measure of heparin effect during pregnancy.

Delivery—LMW heparins should be stopped at the time of delivery. After delivery, heparin should be restarted along with warfarin. Warfarin should never be started without heparin coverage as warfarin skin necrosis can occur in this situation. Mothers on warfarin can nurse because only an inactive form of warfarin is secreted in the breast milk. Warfarin should be continued at an INR of 2.0 - 3.0 for at least a total of six months of therapy. Women with thrombosis in the first trimester should be treated for the duration of the pregnancy and for six weeks after delivery.

Evaluation for Hypercoagulable State

All women who have a deep venous thrombosis during pregnancy should be evaluated for a hypercoagulable state. Many inherited and acquired hypercoagulable states will first manifest themselves during pregnancy. There are several arguments in favor of a specific diagnosis. One is that finding a specific defect would mandate whether to continue therapy with anticoagulant after delivery. Concentrates of antithrombin III are now available and concentrates of protein C and protein S are being tested in clinical trials. These concentrates can be employed as replacement therapy during surgeries or delivery. Patients who are known to have inherited thrombotic disorders may have relatives who would benefit from diagnosis and treatment. Lastly, the finding of a specific factor deficiency can influence the duration of anticoagulant therapy.

Patients should be screened for these conditions 3 weeks after warfarin is stopped to allow proteins C and S levels to return to baseline. Since levels of many proteins change during pregnancy (especially a marked decrease in protein S) it is best not to measure levels then. We currently screen for the following:

- Protein C activity.
- Free protein S levels.
- Hereditary resistance to activated protein C.
- Prothrombin gene mutation.
- Antithrombin III activity.
- Anticardiolipin antibodies.
- Lupus inhibitors.
- Homocysteine level.

Table 28.5. Prophylaxis

- Previous deep venous thrombosis—Not currently being anticoagulated
  - **Dalteparin** 5000 units every 12 hours, or
  - **Enoxaparin** 40 mg every day
- Patient currently being anticoagulated
  - **Enoxaparin** 1 mg/kg every 12 hours to achieve levels 0.7-1.2 four hours after injection, or
  - **Dalteparin** 100 units every 12 hours to achieve levels 0.7-1.2 four hours after injection
- Patients with identified hypercoagulable states but no history of thrombosis
  - Antithrombin III deficiency
    - **Enoxaparin** 1 mg/kg every 12 hours to achieve levels 0.7-1.2 four hours after injection, or
    - **Dalteparin** 100 units every 12 hours to achieve levels 0.7-1.2 four hours after injection
  - All others
    - **Dalteparin** 5000 units every 12 hours, or
    - **Enoxaparin** 40 mg every day

Prophylaxis (Table 28.5)

Previous Deep Venous Thrombosis

These women are at high risk for recurrence and should receive prophylaxis. Most women with a history of thrombosis should receive prophylaxis for the duration of the pregnancy. Woman with a history of an non-estrogen related "provoked" DVT may only need prophylaxis for delivery and 6 weeks postpartum. An example of this would be a patient who suffered a DVT after a leg fracture.

Most experience is with enoxaparin 40 mg every day or with dalteparin 5,000 - 7,500 units every day. Warfarin is given for 6 weeks after delivery with an INR goal of 2.0 - 3.0.

Prosthetic Cardiac Valves

These patients should have their therapy changed to low molecular weight heparin at therapeutic doses as soon as the pregnancy is diagnosed. The best form of anticoagulation remains controversial. Many cases of valve thrombosis with both heparin and LMWH have been reported, but most of these have been associated with very inadequate heparin dosing. However, despite aggressive anticoagulation, the risk of valve thrombosis does remain high, and women with prosthetic valves should be counselled about the risks of pregnancy.

Women with Hypercoagulable States but no History of DVT

Probably all women who have a hypercoagulable state should be given prophylaxis during pregnancy. However, the duration of prophylaxis is controversial. All women should receive prophylaxis if they undergo a caesarian section. Then women should receive prophylaxis for 4-6 weeks after delivery.

Special Issues

Women with Antiphospholipid Antibodies (APLA)

Women with APLA and thrombosis should be aggressively anticoagulated during pregnancy. However, the management of women with APLA without thrombosis is extremely controversial. The use of heparin plus low-dose aspirin has been shown to be more effective than aspirin alone in patients with APLA. It is not known whether the aspirin is really necessary but until this is studied, combination therapy should be used. Women with persistent high-titer APLA with negative pregnancy history or thrombotic history do appear to be at risk for getting complications and should also receive prophylaxis.

Women Currently Anticoagulated Who Want to Get Pregnant

There are several treatment options:

1. Stop the anticoagulation. This is obviously the least desirable but this may be a useful time to review the indications for the patient's anticoagulation.
2. Change the patient to low molecular weight heparin while the couple is trying to conceive. This is the most "desirable" as far as risk to the child but carries the chance that a women may be on a very long course of LMWH.
3. Frequent pregnancy checks and immediate conversion to heparin when positive. This minimizes the risk during the most dangerous time of warfarin therapy for the child.

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CHAPTER 29

Pediatric Thrombosis

Introduction

Thrombosis is rare in children, but when it occurs two peaks of higher incidence are seen. One peak is soon after birth and the second is in the teenage years. Certain groups of patients are also at higher risk of thrombosis. Pediatric patients with cardiac disease have an increased risk of stroke, patients in pediatric ICU have an increased risk of thrombosis, and children who have catheters are at high risk for thrombosis.

Ranges of Normal

The levels of many coagulation proteins are different in pediatric populations. Most coagulation protein levels are low at birth and slowly rise to adult range over the first year of life. However, levels of vitamin K-dependent proteins don't completely rise to the adult range until the teenage years of life. Levels of antithrombin and proteins C and S are significantly lower at birth with protein C levels remaining lower than adult range until the teenage years. It is important when interpreting laboratory values in younger patients to use age-specific normal ranges.

Deep Venous Thrombosis and Pulmonary Embolism

Venous thrombosis is unusual in children; the vast majority of cases are secondary to other disease processes such as nephrotic syndrome. Inherited hypercoagulable states do not appear to play the major role in provoking pediatric venous thrombosis but may increase risk in synergy with acquired risk factors. Although pediatric studies are lacking, the use of doppler ultrasound remains the first choice for diagnostic tests. There is no data regarding the utility of D-dimers in the pediatric population; until this data is available this test should not be used. Likewise, there is little data regarding the use of CT scan in the diagnosis of pulmonary embolism and a negative scan should lead to further testing. Ventilation/perfusion scans are better studied and are useful for diagnosis of PE in this population.

Treatment of neonatal venous thrombosis remains controversial and is best reserved for symptomatic disease. For older children with secondary thrombosis three months of anticoagulation may be used, and for the rare child with idiopathic thrombosis, therapy should be extended for six months.

Catheter-Related Thrombosis

As in adults, the use of catheters in children is associated with a high rate of venous thrombosis. There is a high incidence of postphlebitic syndrome with resultant abnormal venous anatomy. A unique complication of upper extremity central venous line thrombosis is right atrial thrombosis.

Hemostasis and Thrombosis, 2nd Edition, by Thomas G. DeLoughery.

The umbilical artery and vein are unique sites used for catheterization in newborns. Clinically apparent thrombosis rates for umbilical vein catheters ranges from 10-20%. Long-term complications include portal hypertension and varices. Thrombosis of the umbilical artery appears to be more rare but may be associated with severe complications such as renal or mesenteric artery thrombosis or even complete aortic occlusion.

The least sensitive test for thrombosis is ultrasound, with angiography being most sensitive. Three months of therapy are recommended for treatment of venous line thrombosis, and if the line is still required, prophylactic anticoagulation to an INR of 1.5-1.8 or prophylactic LMWH for the duration of the line placement is recommended. Arterial line thrombosis mandates the removal of the line. If significant ischemia is occurring, catheter-directed thrombolytic therapy should be considered.

Renal Vein Thrombosis

Renal vein thrombosis is most common during the first month of life. Conditions which predispose to renal vein thrombosis are cyanotic heart disease, dehydration and sepsis. In older children nephrotic syndrome is associated with thrombosis. Thrombocytopenia, hematuria, renal dysfunction and flank mass are common presenting signs. Diagnosis can be made by ultrasound or by vascular imaging. Therapy remains controversial with conservative therapy recommended for neonates unless the inferior vena cava is involved. Older children with renal vein thrombosis should be anticoagulated indefinitely since this implies a hypercoagulable state.

Pediatric Stroke

Neonatal stroke occurs in about one in 4000 births. Risk factors for neonatal stroke include infection, cardiac disease and hypercoagulable states. Fortunately, the risk of recurrent stroke is low (3-5%) and there is often no need for long-term therapy.

Stroke in older children is less common (4/100,000) but has a much higher recurrence rate of up to 20-40%. Cardiac disease is the leading cause of stroke. Unlike with adult strokes, the presence of classic venous hypercoagulable states seems to be more common in childhood stroke.

Sickle cell anemia is a major risk factor for stroke with a relative risk of up to 400. If untreated, the stroke recurrence rate can be as high as 50%. Sickle cell anemia patients who suffer stroke should be placed on a transfusion program to keep their percentage of hemoglobin S under 30%.

Chickenpox (varicella zoster) is associated with an angiopathy which can lead to stroke. Over time this angiopathy may resolve. Varicella infections have also been associated with an acquired antibody to protein S and this may also play a role in stroke formation. Another infectious cause of stroke is vascular inflammation from meningitis or encephalitis.

Dissection is also a frequent cause of stroke which in some series is found in up to one-fifth of pediatric patients. Dissection should be looked for especially in children with a history of trauma or in those presenting with stroke and carotidynia. Therapy with heparin for six months may be warranted in these patients.

Cerebral vein thrombosis in children is most often seen in association with other disorders. Most occur in the neonatal period and are related to birth complications, dehydration or sepsis. In older children, serious illness such as connective tissue disease, cancer or cardiac disease are the most common risk factors. As in adults,

most patients will have signs and symptoms of increased intracranial pressure. Many of these children will also have underlying inherited hypercoagulable states. Another major risk factor for cerebral vein thrombosis is head and neck infection. Neonates probably should be treated conservatively. Older children, as with adults, appear to benefit from anticoagulation. For cerebral vein thrombosis with a clear secondary cause, six months of therapy should be given. For idiopathic cerebral vein thrombosis, a longer course of therapy should be considered.

Homozygous Protein C or S Deficiency

Homozygous protein C deficiency should be suspected when purpura fulminans occurs hours to days after delivery. Other presenting symptoms include blindness due to retinal thrombosis and hemorrhage, central nervous system hemorrhage, severe DIC, and large vessel thrombosis. Diagnosis is made by proving absence of protein C in the neonate and by demonstrating that the parents are heterozygous for protein C deficiency. Several choices for therapy exist. Fifteen mg/kg of FFP is infused every 12 hours. Protein C concentrate offers more specific therapy and is dosed at 20-60 units to achieve a peak level of 60% (0.6 units/ml). Once the patient has stabilized and all skin lesions have healed, oral anticoagulation is started. Homozygous protein S deficiency is rare but is treated with FFP and oral anticoagulants.

Cardiac Disease

Children with mechanical heart valves should be anticoagulated with warfarin to a target INR of 3.0 (range 2.5-3.5) with the addition of aspirin for patients with recurrent thrombosis.

Need for antithrombotic therapy after surgery for congenital heart disease is less clear. Patients with Blalock-Taussig shunts appear to benefit from a short course of warfarin followed by aspirin at a dose of 1-5 mg/kg/day. There is a high rate of late thrombosis after Fontan operations, ranging from 3-20%. The ideal prophylactic therapy is currently under study in a large trial comparing aspirin (5 mg/kg/day) to warfarin. Patients who have suffered a thrombosis should be treated with warfarin. In Fontan patients with malabsorption syndrome, management of warfarin can be a problem due to erratic INRs and INRs that do not reflect the level of anticoagulation (due to loss of factor VII). LMWH is useful in these patients.

Pediatric Use of Antithrombotic Agents

Antiplatelet Therapy

Despite the need for and use of antiplatelet therapy in children, little data exists regarding dosing of these agents. For mechanical valves, aspirin doses in the range of 6-20 mg/kg/day have been used. No data exists on dosing ticlopidine, clopidogrel, or GP IIb/IIIa inhibitors in children.

Heparin and Heparin-Induced Thrombocytopenia

Use of standard heparin is challenging in young children because of their low levels of antithrombin and other differences in the coagulation system. The bolus is with 75 units/kg. The maintenance dose for children under one is 28 units/kg/hr, and for children older than one is 20 units/kg/hour. Measurement of anti-Xa levels is preferable to using the aPTT.

Although once considered rare, heparin-induced thrombocytopenia (HIT) can occur in neonates and children. Due to the need for frequent catheterization with

Table 29.1. Pediatric dosing of heparin and LMWH heparin

Standard heparin
Bolus: 75 units/kg
Maintance:
< 1 year: 28 units/kg/hr
>1 year: 20 units/kg/hr
Adjust to aPTT range that reflects heparin level of 0.35-0.70 anti-Xa units
Enoxaparin
Treatment dose:
< 5 kg: 1.5 mg/kg every 12 hours
> 5 kg: 1.0 mg/kg every 12 hours

attendant heparin exposure, HIT is common especially in children with cardiac disease.

Low Molecular Weight Heparin

As with adult patients, LMWH offers several advantages in children, especially in ease of dosing and monitoring. Very small children (under 5 kg and/or under two months of age) have higher dosage requirements for LMWH. The best studied agent is enoxaparin, with the dosing of 1 mg/kg/q12 hours for age over 2 months, and 1.5 mg/kg/q12 for under 2 months. Anti-Xa levels should be checked four hours after the second or third dose, especially in the younger patients.

Warfarin

Despite often having lower levels of vitamin K-dependent proteins, children require more warfarin per unit of body weight than adults. In children less than one year of age, the average warfarin dose was 0.33 mg/kg, while in children age 13-16 the dose was 0.09 mg/kg. In addition, the use of other medicines, nutritional supplements and concurrent illness can cause the dose to vary greatly, requiring close monitoring. One suggested approach is to start with a loading dose of 0.2 mg/kg with dosage adjustments based on a daily INR checks.(Table 29.2)

Table 29.2. Pedatric dosing of warfarin

Day 1: Warfarin 0.2 mg/kg
Day 2-4 Protocol

INR	**Action**
1.1 -1.3	Repeat day 1 dose
1.4 -1.9	50% of day 1 dose
2.0 - 3.0	50% of day 1 dose
3.1 - 3.5	25% of day 1 dose
> 3.5	Hold until INR < 3.5, then 50% of previous dose

Maintance Guidleines

INR	**Action**
1.1 -1.3	Increase dose by 20%
1.4 -1.9	Increase dose by 10%
2.0 - 3.0	No change
3.1 - 3.5	Decrease by 10%
> 3.5	Hold until INR < 3.5, then 20% of previous dose

Table 29.3. Pediatric dosing of thrombolytic therapy

Urokinase:	Load with 4400 units/kg and infuse 4400 units/kg/hr for 4 - 6 hours
Streptokinase:	Load with 2000 units/kg and infuse 2000 units/kg over 4 - 6 hours
tPA:	No loading dose. Infuse 0.1 - 0.6 mg/kg for 6 hours

Thrombolytic Therapy

The most studied thrombolytic agent in children is tissue plasminogen activator (tPA). For arterial thrombosis the dose of 0.3 mg/kg/hr was associated with clot resolution in most cases. Although higher doses (0.5 mg/kg/hr) are commonly recommended for neonates, recent evidence suggests that 0.3mg/kg/hr is effective.

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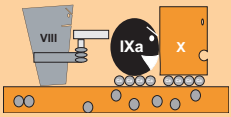

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