22
CHAPTER

THROMBOPHILIAS

Jessica B. Michaud and Canice A. Coan

INTRODUCTION

Testing for thrombophilias, also called *hypercoagulable states*, is used to determine patients' risk of thrombosis. Thrombophilias, which can be inherited or acquired, are associated with venous thromboembolism and, less commonly, with arterial thromboembolism as seen in antiphospholipid syndrome (APS) (see **Table 22-1**).[1] Thrombophilia testing is controversial with regard to when, who, and what to test, and how positive thrombophilia tests influence treatment decisions. Because several methods can be used for a given test for hypercoagulability, it is important to know which test is used and any of its potential downfalls. Testing should be considered if the results alter the management approach.

BASICS OF THE THROMBOPHILIAS

TABLE 22-1: **Basic Information about Thrombophilias**

Thrombophilia Category	Basic Information about the Thrombophilia
Increased levels or function of natural procoagulants	Activated protein C resistance occurs when factor Va is resistant to inactivation by activated protein C: • 90-95% of activated protein C resistance is caused by the factor V Leiden mutation.[1-3] • Factor V Leiden mutation is a point mutation on the factor V gene that codes for the cleavage site of factor V by activated protein C.[2,3]
	Prothrombin G20210A mutation on the prothrombin gene causes elevated circulating levels of otherwise normal prothrombin.[2,4,5]
	Elevated levels of otherwise normal factors, especially of factors VIII, IX, and XI, can also result in a thrombophilia[2,6]; the cause is unknown but could be genetic.[2]

(continued)

TABLE 22-1: **(Continued)**

Thrombophilia Category	Basic Information about the Thrombophilia
Deficiencies of the natural anticoagulants	Antithrombin (formerly termed antithrombin III) inhibits factor IIa (thrombin), factor Xa, and other factors.[2]
	Activated protein C, with its cofactor protein S, inhibits factors Va and VIIIa.[2,4]
	Deficiencies of antithrombin, protein C, and protein S are caused by >100 mutations each, making genetic testing impractical.[4]
APS	APS is an acquired thrombophilia where auto-antibodies bind to phospholipids (e.g., cardiolipin), phospholipid-binding proteins (e.g., β_2-glycoprotein [GP] I), or both.[2]
	aPL include positive lupus anticoagulant tests, elevated anticardiolipin antibody levels, and/or elevated anti-β_2-GPI levels.
	APS is its own distinct disorder but may coexist with rheumatologic diseases such as systemic lupus erythematosus.
	The presence of aPL is associated with anticoagulant (hence the term *lupus anticoagulant*) and procoagulant effects on the clotting system, but the usual eventual net result is a procoagulant effect.[7]
	APS may involve recurrent pregnancy loss, chronic thrombotic microangiopathy (causing organ dysfunction), cardiac valvulopathy, thrombocytopenia, livedo reticularis, and a potentially fatal catastrophic form, in addition to venous and arterial thromboembolism.[7]
Hyperhomocysteinemia	Hyperhomocysteinemia, the elevation of the amino acid homocysteine in the plasma, signifies increased risk of arterial or venous thrombosis. Mutations in several genes that code enzymes involved in homocysteine metabolism can lead to hyperhomocysteinemia.[8] It is not clear whether hyperhomocysteinemia causes thrombosis or whether venous thrombosis and ischemic cardiovascular disease elevate homocysteine.[1,9]

aPL: antiphospholipid antibodies, APS: antiphospholipid syndrome

THROMBOPHILIA PREVALENCE AND RISK FOR THROMBOSIS

See **Table 22-2** for more information on prevalence and risk of thrombosis.[10]