How to Cite:
Almuhaysh, M. A., Alsadun, J. S., Almulhim, M. M., Almousa, M. M. A., Hadadi, A. M., Aljaafari, O. A., Alhussain, A. H., Alquwayi, W. A., Alkuwaiti, Y. A. A., & Almehainy, A. M. (2022). Thrombophilia screening in clinical pathology: Guidelines and controversies. *International Journal of Health Sciences*, *6*(S10), 1890–1907. https://doi.org/10.53730/ijhs.v6nS10.15194

Thrombophilia screening in clinical pathology: Guidelines and controversies

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International Journal of Health Sciences E-ISSN 2550-696X © 2022.
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Manuscript submitted: 1 Jan 2022, Manuscript revised: 9 Jan 2022, Accepted for publication: 15 Jan 2022

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***Abstract*---Background**: Thrombophilia screening is crucial in assessing the risk of venous thromboembolism (VTE), particularly in patients with a history of VTE. Clinical guidelines recommend targeted testing based on management implications and clinical context, including factors like surgery, malignancy, and hormonal status. **Aim**: This review evaluates the significant laboratory factors affecting the interpretation of thrombophilia test outcomes, specifically focusing on inherited and acquired thrombophilias associated with VTE. **Methods**: The review discusses common thrombophilias, including factor V Leiden, prothrombin mutations, deficiencies in protein C, protein S, and antithrombin, as well as antiphospholipid antibodies. It emphasizes pre-analytical variables influencing diagnostic accuracy and describes recommended laboratory protocols for specimen collection, processing, and testing. **Results**: Key findings indicate that genetic mutations and deficiencies significantly elevate VTE risk in various populations. The accuracy of functional assays is influenced by factors such as specimen handling, anticoagulant therapy, and the presence of interfering substances. **Conclusion**: Proper interpretation of thrombophilia testing is essential for effective patient management. Understanding the impact of laboratory variables is crucial for minimizing diagnostic errors and ensuring accurate assessment of thrombotic risks.

***Keywords*---**thrombophilia, venous thromboembolism, laboratory factors, genetic mutations, diagnostic accuracy.

Introduction

Evaluations for both inherited and acquired thrombophilias are routinely conducted among patients who experience venous thromboembolism (VTE). Most clinical guidelines advocate for testing only when the outcomes will directly impact management strategies [1, 2]. The interpretation of these results must consider various clinical elements that may affect VTE risk, including recent surgical procedures, hospitalization, malignancy, obesity, and hormonal status. This review will specifically emphasize the significant laboratory factors that are essential for accurately interpreting thrombophilia test outcomes. The discussion will encompass only those thrombophilias that have been consistently identified as risk factors for VTE, namely: mutations in the factor V and prothrombin genes, deficiencies in the natural anticoagulants protein C, protein S, and antithrombin, as well as acquired antiphospholipid antibodies, including lupus anticoagulant, anti-β2-glycoprotein-I antibody, and anticardiolipin antibody. The prevalence of these thrombophilias within the general Caucasian population and their associated relative risk for the initial occurrence of VTE are crucial for understanding their clinical implications.

Pre-analytical variables can significantly influence the diagnostic precision of routine coagulation assays that form the foundation of numerous thrombophilia tests [3]. These variables may pertain to aspects such as specimen collection, transport, processing, and storage. For functional clot-based assays, venous blood should be collected into one-tenth volume of 3.2% trisodium citrate, with careful consideration given to the order of draw and the technique of tourniquet application. Samples are ideally transported at room temperature and should be tested within four hours of collection. Centrifugation must yield a residual platelet count of less than 10×10^9/L in platelet-poor plasma (PPP), with routine checks on platelet counts every 6 to 12 months to ensure the proper execution of centrifugation techniques [4]. PPP can be preserved at –20°C for two weeks or at –70°C for a minimum of six months. It is important to note that hemolysis, icterus, and lipemia may interfere with results due to spectral overlap when employing optical methods [3].

Factor V Leiden (FVL) represents a point mutation within the factor V (FV) gene and is recognized as the most prevalent hereditary thrombophilia among Caucasian populations. This mutation results in the substitution of glutamine for arginine at amino acid position 506, effectively removing the cleavage site for activated protein C (APC), which normally cleaves activated FV (FVa) and leads to sustained FVa activity. Testing for FVL may be conducted via functional clot-based assays that assess APC resistance or through direct DNA-based assays that identify the FVL mutation. APC resistance assays are amenable to automation and are cost-effective, making them suitable for initial screening procedures. These functional clotting assays evaluate the ratio of clotting time in the presence versus absence of APC, where a reduced ratio that falls below the laboratory's established threshold indicates APC resistance. The original assay method compared activated partial thromboplastin time (APTT) with and without exogenous APC; however, this approach may yield overlapping results between FVL carriers and non-carriers [5, 6]. Therefore, a modified assay is typically preferred, wherein patient plasma is diluted 1:5 with FV-deficient plasma to enhance both sensitivity and specificity [7]. This adjustment accounts for variations in factor levels due to factors such as vitamin K antagonists (VKAs), liver dysfunction, acute phase reactants, pregnancy, and the oral contraceptive pill (OCP) [8]. Furthermore, the reagents in this modified assay contain a heparin neutralizer, allowing for the mitigation of heparin interference within its therapeutic range, typically up to approximately 1 U/mL. Elevated heparin concentrations may, however, produce a falsely increased APC resistance ratio [9].

An alternative functional assay employs Russell's viper venom (RVV-X) to initiate coagulation, comparing the clotting time post-incubation with Southern copperhead venom—which activates endogenous protein C—against the clotting time of untreated plasma [9]. Pre-dilution with FV-deficient plasma can similarly be applied to eliminate interference stemming from deficiencies in other clotting factors, as well as protein C or protein S [10]. The RVV-X methodology bypasses the intrinsic pathway by directly activating FX, thereby enhancing specificity. The test reagents include heparin neutralizers and high phospholipid concentrations, which mitigate interference from lupus anticoagulants (LAC) [2]. Both APTT and RVV-X methods may be susceptible to direct oral anticoagulants (DOACs), which directly inhibit FXa (apixaban, edoxaban, rivaroxaban) or thrombin (dabigatran),

potentially leading to falsely normal results. Interference from direct FXa inhibitors can be minimized by employing an FV activator (RVV-V) and Noscarin to trigger coagulation. Directly activating FV assists in circumventing FXa, rendering the test insensitive to the presence of direct Xa inhibitors. This approach also utilizes heparin neutralizers and demonstrates insensitivity to LAC, as Noscarin functions independently of phospholipids [11, 12].

Investigations for both inherited and acquired thrombophilias are commonly conducted among individuals who have experienced venous thromboembolisms (VTE). Most clinical guidelines stipulate that testing should be undertaken only when the results are likely to influence management decisions [1, 2]. Moreover, the interpretation of these results must be contextualized within clinical variables that affect the VTE risk, including recent surgical procedures, hospitalizations, malignancies, obesity, and hormonal influences. This review will concentrate solely on the critical laboratory considerations essential for interpreting thrombophilia test outcomes. The discussion will include only those thrombophilias that have consistently been identified as risk factors for VTE: mutations in the factor V and prothrombin genes, deficiencies in natural anticoagulants such as protein C, protein S, and antithrombin, as well as acquired antiphospholipid antibodies, which include lupus anticoagulant, anti-β2-glycoprotein-I antibody, and anticardiolipin antibody.

The prevalence of various thrombophilias within the general Caucasian population and their corresponding relative risks for initial VTE are as follows: Factor V Leiden heterozygosity is present in 6% of the population, with a relative risk of 2.7 (95% CI: 1.3–5.6). Prothrombin gene heterozygosity occurs at a prevalence of 3.9%, with a relative risk of 1.7 (95% CI: 0.9–3.1). The prevalence of protein C deficiency is 0.8%, associated with a relative risk of 3.8 (95% CI: 1.3–10), while protein S deficiency has a prevalence of 0.7% and a relative risk of 1.7 (95% CI: 0.4–6.9). Antithrombin deficiency is found in 0.2% of the population, presenting a relative risk of 5.0 (95% CI: 0.7–34). Lupus anticoagulant is present in 0.9% of individuals, correlating with a relative risk of 3.6 (95% CI: 1.2–10.9). The anti-β2-glycoprotein-I antibody occurs in 3.4% of the population with a relative risk of 2.4 (95% CI: 1.3–4.2), and anticardiolipin antibody is found in 1% of the population, with a relative risk of 1.5 (95% CI: 0.6–3.6). Here, CI denotes confidence interval, and VTE signifies venous thromboembolism.

General Pre-Analytical Considerations

Pre-analytical factors can significantly influence the diagnostic precision of standard coagulation assays that serve as the foundation for numerous thrombophilia evaluations. These variables may stem from processes related to specimen collection, transport, processing, and storage [3]. For functional clot-based assays, venous blood should be collected into a tube containing one-tenth the volume of 3.2% trisodium citrate, with careful attention to the order of draw and tourniquet technique. Specimens should be transported at ambient temperature and are generally suitable for testing within four hours post-collection. Centrifugation should aim for a residual platelet count of less than 10×10^9/L in the platelet-poor plasma (PPP), with platelet counts verified every six to twelve months to ensure proper centrifugation protocols [4]. PPP can be

preserved at –20°C for two weeks or at least –70°C for up to six months. Interference from conditions such as haemolysis, icterus, and lipaemia may occur, particularly when utilizing optical methods due to spectral overlap [3].

Factor V Leiden

Factor V Leiden (FVL) is recognized as the most prevalent hereditary thrombophilia in Caucasian populations and is a result of a point mutation in the factor V (FV) gene. This mutation involves the substitution of glutamine for arginine at amino acid position 506, which eliminates the cleavage site for activated protein C (APC). Consequently, this allows for sustained activity of activated FV (FVa). Testing for FVL can be conducted via functional clot-based assays to assess APC resistance or through direct DNA-based assays to identify the FVL mutation.

APC resistance assays are automated and cost-effective, rendering them appropriate for initial screening. These functional clotting assays evaluate the ratio of clotting times in the presence and absence of APC, with a reduced ratio below the laboratory's established threshold indicating APC resistance. The original assay method compared activated partial thromboplastin time (APTT) with and without exogenous APC; however, this method may yield overlapping results for both carriers and non-carriers of FVL [5, 6]. Consequently, a modified assay is typically recommended, in which patient plasma is diluted 1:5 with FV-deficient plasma, enhancing both sensitivity and specificity [7]. This modification corrects for altered factor levels due to factors such as vitamin K antagonists (VKAs), liver dysfunction, acute phase reactants, pregnancy, and oral contraceptive pills (OCP) [8]. The reagents in the modified assay include a heparin neutralizer to mitigate heparin interference within its therapeutic range, generally up to approximately 1 U/mL; higher heparin concentrations may produce a falsely elevated APC resistance ratio [9].

An alternative functional assay employs Russell's viper venom (RVV-X) to initiate coagulation, comparing the clotting time following incubation with southern copperhead venom, which activates endogenous protein C, to that of untreated plasma [9]. Pre-dilution with FV-deficient plasma, akin to APTT-based assays, may be utilized to eliminate interference from deficiencies in other clotting factors, protein C, or protein S [10]. The RVV-X methodology bypasses the intrinsic pathway by directly activating FX, thereby enhancing specificity. Reagents utilized in this testing methodology include heparin neutralizers and high phospholipid concentrations that can diminish interference from lupus anticoagulants (LAC) [2]. Both APTT and RVV-X methodologies may be affected by direct oral anticoagulants (DOACs), which directly inhibit FXa (e.g., apixaban, edoxaban, rivaroxaban) or thrombin (e.g., dabigatran), potentially leading to false normal results.

Interference from direct FXa inhibitors can be minimized by employing FV activator (RVV-V) and Noscarin to trigger coagulation. The direct activation of FV assists in bypassing FXa, rendering the test insensitive to direct FXa inhibitors. This method also incorporates heparin neutralizers and is unaffected by the presence of LAC, as Noscarin operates independently of phospholipids [11, 12].

Potential Interferences by Anticoagulants and Effects of Clinical Factors on Thrombophilia Testing

Heparin may lead to a false increase in activated protein C resistance, while vitamin K antagonists can result in a false decrease, as can direct anti-FXa and direct thrombin inhibitors. Pregnancy and oral contraceptive use are associated with false increases, while acute inflammation may cause variable effects. Liver disease typically leads to false decreases. Lupus anticoagulant can cause false positives, with the effects being transient in the context of pregnancy and oral contraceptive use. Factor V Leiden DNA testing is unaffected by any of these factors.

Prothrombin gene DNA testing remains stable across these variables. Clot-based assays for protein C can yield false increases due to heparin, vitamin K antagonists, and direct anti-FXa inhibitors, while direct thrombin inhibitors can also result in false increases. These assays may also yield false decreases during acute inflammation, liver disease, and the presence of lupus anticoagulant. In contrast, chromogenic assays for protein C are susceptible to false decreases from vitamin K antagonists and liver disease. Similar variability exists in the clot-based and immunological assays for protein S, with false increases noted in the presence of heparin and false decreases due to vitamin K antagonists, lupus anticoagulant, and acute inflammation. Antithrombin assays, whether thrombin-based or FXa-based, may exhibit false decreases due to heparin, vitamin K antagonists, and acute inflammation. The presence of lupus anticoagulant similarly affects these results. Anticardiolipin antibodies and anti-β2-glycoprotein-I antibodies can also present variable interference, particularly during transient conditions such as pregnancy and acute inflammation.

Direct DNA-based assays are unaffected by variables that may influence functional assays for activated protein C (APC) resistance. The detection of the single nucleotide mutation responsible for factor V Leiden (FVL) previously necessitated a two-step procedure. This involved polymerase chain reaction (PCR) amplification of the region surrounding the mutation, followed by analysis of the amplification products through various allele-discriminatory techniques. This manual, labor-intensive process has been largely supplanted by semi-automated, one-step direct mutation testing methodologies, frequently employing multiplex assays that simultaneously detect prothrombin gene mutations [13].

It is noteworthy that DNA-based testing may overlook rare variants of APC resistance, such as FV Cambridge (R306T; p.Arg334Thr) and FV Hong Kong (R306G; p.Arg334Gly); however, these variants do not independently constitute clear risk factors for thrombosis [14]. Some algorithms advocate for an initial screening utilizing a functional APC resistance assay, followed by a confirmatory DNA-based test to validate the presence of the FVL mutation [9]. Nevertheless, as the cost of molecular testing has decreased and availability has increased, along with the diminished likelihood of interferences in DNA-based assays, laboratories are compelled to establish their testing protocols according to local capabilities and resources.

Prothrombin Gene Mutation

A single nucleotide mutation at position 20210 of the prothrombin gene (G20210A) leads to enhanced synthesis of prothrombin [15]. Increased prothrombin levels correlate with heightened thrombin generation and an elevated risk of venous thromboembolism (VTE) [16]. Due to considerable variability in plasma prothrombin levels, overlapping values between carriers and non-carriers frequently occur. Consequently, plasma prothrombin level assays are not diagnostic. Instead, DNA-based techniques, akin to those utilized for detecting FVL mutations, are employed and often executed concurrently [13]. Testing methods must effectively differentiate between the pathogenic G20210A mutation and rare polymorphisms lacking a definitive association with VTE [17].

Protein C Deficiency

Protein C, a vitamin K-dependent serine protease activated by thrombin, cleaves factors FVa and FVIIIa in the presence of its cofactor, protein S. Congenital protein C deficiency is transmitted as an autosomal dominant trait, most commonly resulting from a reduced production of functional protein (type I deficiency). Type II deficiencies, which are less common, arise when normal amounts of dysfunctional protein are produced [18]. Functional assays, whether clot-based or chromogenic, are favored for diagnosing protein C deficiency over immunoassays that only measure antigen levels, as they cannot identify type II deficiencies [19]. Clot-based functional assays assess protein C activity following in vitro activation by southern copperhead viper venom extract (Protac). Patients exhibiting diminished APC are less capable of cleaving FVa and FVIIIa, leading to a shortened clotting time as measured by activated partial thromboplastin time (APTT). Consequently, inflammatory conditions that elevate FVIII levels may produce lower protein C results, as can APC resistance stemming from FVL. Factors extending APTT, including lupus anticoagulant (LAC), heparin, or direct oral anticoagulants (DOAC), may yield falsely elevated protein C results and false negatives [18]. Utilizing RVV-based assays may mitigate the impact of elevated FVIII levels, as the venom directly activates factor X and may be less influenced by FVL [20]. Chromogenic assays utilize patient APC to cleave a synthetic substrate, subsequently liberating a chromogenic substrate that can be detected spectrophotometrically. Chromogenic assays are generally preferred due to their lower variability and enhanced specificity, as they are less susceptible to the interferences observed in clot-based assays [21]. However, certain rare type II variants can only be identified through clot-based assays, particularly mutations affecting phospholipid interactions, since chromogenic assays are independent of phospholipids [19]. Additionally, falsely elevated results may occur in the presence of other enzymes that cleave the chromogenic substrate, such as tissue plasminogen activator, which is often present at elevated levels in patients recently undergoing therapeutic thrombolysis [19].

Before diagnosing congenital protein C deficiency, it is essential to rule out acquired causes of reduced protein C. Liver disease, vitamin K deficiency, and oral vitamin K antagonists (VKAs) result in decreased protein C synthesis. For patients receiving oral VKAs, protein C levels may be less affected when assessed via chromogenic assays compared to clot-based assays [22]; however, testing for

protein C activity should ideally be conducted at least ten days post the last VKA dose [18]. Recent or active thrombosis, surgical interventions, and disseminated intravascular coagulation (DIC) result in increased consumption of protein C. Additionally, elevated protein C activity can be observed during pregnancy and with the use of oral contraceptive pills (OCP) [23]. The reference range for pediatric patients is critical to consider, as protein C levels are low at birth, rising to approximately 50% by six months and remaining below adult values until at least 16 years of age [24]. More than 160 distinct mutations in the PROC gene have been identified in patients with congenital protein C deficiency, predominantly involving single base changes resulting in missense and nonsense mutations [25]. However, gene analysis remains limited in availability, and no strong correlation has been established between PROC gene mutations and thrombosis [18].

Protein S Deficiency

Protein S functions as a vitamin K-dependent cofactor for APC, mediating the degradation of FVa and FVIIIa. Approximately 60% of total protein S is bound to the acute phase protein C4b-binding protein (C4bBP), which exerts minimal or no anticoagulation effect, while the remaining 40% of the free unbound fraction is responsible for anticoagulant activity [26]. Inherited protein S deficiency manifests as an autosomal dominant condition, characterized by three recognized forms: type I quantitative defects featuring reduced levels of both total and free protein S; rare type II qualitative defects where normal antigen levels coexist with diminished cofactor activity; and type III quantitative defects with normal total protein S levels yet reduced free protein S. All three subtypes exhibit a similar clinical phenotype [27]. Protein S testing can be performed using either immunoassays to quantify antigen levels or functional clot-based methods. Immunological techniques, such as latex immunoassays or enzyme-linked immunosorbent assays (ELISA), accurately quantify free protein S [28]. Similar assays can also measure total protein S to differentiate between type I and type III deficiencies, although they provide limited utility in patient management due to their comparable clinical phenotypes. Nonetheless, immunoassays will not identify the 5% of protein S deficiency cases resulting from type II qualitative defects. Thus, functional assays are necessary for accurate diagnosis, with APTT-based tests being the most commonly employed. Patient plasma is incubated with protein S-deficient plasma and either a protein C activator or exogenous APC. The resulting clotting time is proportional to protein S activity as both protein S and APC inactivate FVIIIa and FVa [28]. Some laboratories may utilize alternative prothrombin time (PT) or RVV-based assays. Clot-based protein S assays are typically more prone to technical issues than other clot-based tests, making them susceptible to spurious results and exhibiting poor specificity [27, 29]. Elevated FVIII levels may result in an underestimation of protein S activity; however, this can be mitigated by diluting patient plasma with protein S-deficient plasma [30]. LAC and DOAC may falsely elevate protein S results when using APTT-based assays [28]. Immunological assays are resistant to these interferences, though, similar to most immunoassays, elevated levels of rheumatoid factor or other heterophile antibodies may cause inaccurate protein S measurements [31].

Acquired protein S deficiency can arise from either increased consumption or decreased synthesis, with causes overlapping those of acquired protein C deficiency. Additionally, alterations in C4bBP levels can redistribute protein S levels. Inflammation, OCP use, and pregnancy elevate C4bBP levels, resulting in a lower proportion of free active protein S [23]. A low protein S result should be correlated with inflammatory markers such as FVIII and fibrinogen and confirmed through repeat testing after a minimum of four weeks [28]. Age and gender also influence protein S levels. At birth, total protein S levels are approximately one-third of adult values; however, due to low C4bBP, the majority of protein S exists in its free active form. Total and free protein S levels reach adult values within a few months after birth [24]. Both total and free protein S levels are approximately 15% lower in females than in males, with levels in females increasing with age and menopausal status [32, 33]. Over 130 distinct mutations have been identified in the gene encoding protein S (PROS1), predominantly comprising missense mutations dispersed throughout the coding sequence [34]. As with PROC gene analysis, testing for PROS1 mutations can only be conducted at specialized centers [28].

Antithrombin Deficiency

Antithrombin primarily functions as an anticoagulant by inhibiting thrombin and factor Xa (FXa), with its efficacy significantly enhanced through interactions with heparin. This deficiency is inherited in an autosomal dominant manner and can be attributed to either a type I quantitative mutation that results in decreased antigen levels or a type II qualitative mutation leading to a dysfunctional variant of the protein. Type II deficiencies are further categorized based on the defect's location: reactive site (RS), heparin binding site (HBS), and pleiotropic defects. Both RS and HBS defects maintain normal antigen levels, while pleiotropic defects show diminished levels and activity. Patients with HBS mutations exhibit a lower risk of thrombosis compared to other variants, suggesting that identifying this mutation via progressive activity—characterized by enhanced activity with extended incubation—might hold clinical significance (35, 36).

Functional chromogenic assays are employed to diagnose antithrombin deficiency, effectively detecting both type I and type II forms; however, they cannot differentiate between them or their specific qualitative subtypes. These assays can utilize thrombin or FXa. In thrombin-based assays, heparin and excess thrombin are introduced to the patient's antithrombin, leading to thrombin inactivation by antithrombin, which allows the remaining thrombin to cleave a chromogenic substrate. Consequently, the level of antithrombin activity correlates inversely with the spectrophotometric signal observed. Conversely, FXa-based assays replace thrombin with FXa. Direct oral anticoagulants (DOACs) may artificially elevate antithrombin activity results, depending on the type of assay; for instance, direct thrombin inhibitors influence thrombin-based assays but not FXa-based ones, while the reverse is true for direct FXa inhibitors (38, 39).

An assay designed to detect progressive activity, although not commonly available, can help differentiate HBS defects from other type II deficiencies by being conducted with prolonged incubation and in the absence of heparin. In this context, HBS variants will exhibit normal activity, unlike other type II variants

(36). To further distinguish between type I and type II defects, immunoassays measuring antithrombin levels can be conducted alongside functional assays. In practice, immunoassays are seldom performed as type II qualitative defects typically display a low activity-to-antigen ratio (40). Acquired reductions in antithrombin levels are more prevalent than inherited forms. Upon detecting low antithrombin levels, it is advisable to repeat testing to rule out transient factors and confirm consistency (37). Conditions like liver disease lead to decreased antithrombin synthesis, often occurring alongside deficiencies in protein C and protein S. The use of L-asparaginase is associated with reduced antithrombin levels due to potential hepatic dysfunction (41). Factors such as recent or active thrombosis, surgery, and disseminated intravascular coagulation (DIC) can elevate consumption rates, while proteinuria may result in antithrombin loss. Although heparin can slightly lower antithrombin levels through increased clearance, this rarely reduces levels below 70% (42). Additionally, antithrombin levels are generally lower during pregnancy and with oral contraceptive pill (OCP) use (43). Newborns exhibit antithrombin levels at approximately two-thirds of adult levels, which typically normalize within six months (44).

The SERPINC1 gene, located on chromosome 1 and comprising seven exons, encodes antithrombin. More than 300 unique mutations linked to antithrombin deficiency have been identified. Type I mutations are generally infrequent and often restricted to individual families, while type II mutations are prevalent in certain populations due to the founder effect (45, 46). DNA testing for antithrombin deficiency remains limited in availability, similar to deficiencies of protein C and protein S (37).

Antiphospholipid Antibodies

For the diagnosis of antiphospholipid syndrome (APS), the persistent presence of lupus anticoagulant (LAC), anti-β2-glycoprotein-I (β2GP-I) antibodies, or anticardiolipin antibodies (ACA) is essential (47). Among these, LAC presence serves as the strongest indicator of APS clinical manifestations (48). Unlike inherited thrombophilias, APS is an acquired condition that also elevates the risk of arterial thrombosis.

Current international guidelines recommend the use of two clot-based assays for LAC detection (49, 50). Commonly employed assays include the dilute Russell viper venom time (dRVVT), known for its high specificity, and activated partial thromboplastin time (APTT) using silica as an activator for heightened sensitivity. Kaolin clotting time is discouraged due to its inconsistent reproducibility compared to other available methods (51). The detection of LAC is performed through a three-step procedure involving screening, mixing, and confirmation. LAC is identified when both the screening and mixing tests exceed the local cutoff value and are validated by the presence of excess phospholipid during the confirmation step. It is critical to utilize platelet-poor plasma (PPP) with a platelet count of $<10\times10^9$/L, as residual platelets' phospholipids may neutralize LAC, resulting in misleadingly normal results. This is especially pertinent for samples that have undergone freezing and thawing, which can disrupt platelet membranes (52). Normalization of results to pooled normal plasma helps mitigate variability among different reagents, instruments, and operators (49).

Transient LACs frequently occur and may arise in contexts such as infection, inflammation, and pregnancy (49, 53). A positive LAC result should always be retested for confirmation after 12 weeks. Concurrent screening of coagulation tests, including prothrombin time (PT), APTT, thrombin time, fibrinogen, and anti-FXa activity, can assist in identifying potential interference from anticoagulation therapies, clotting deficiencies, specific factor inhibitors, and acute phase reactants (49). Most dRVVT reagents contain heparin neutralizers, like heparinase, protamine, or polybrene, which remain effective against heparin levels typically up to 1 U/mL (49). Heparin levels surpassing the reagent's neutralizing capacity may yield false positives (54). Conversely, most APTT reagents lack such neutralizers, as one of the primary roles of APTT testing is to monitor therapeutic unfractionated heparin treatment (55). Testing for LAC while patients are on low molecular weight heparin (LMWH) may yield accurate results, as LMWH has a lesser impact on dRVVT, particularly at trough LMWH levels and in the presence of a heparin neutralizer. However, results may vary based on the LMWH type and its anti-FXa/FIIa ratio (56, 57).

The mixing step can rectify acquired factor deficiencies due to vitamin K antagonists (VKAs) but may lead to false negatives by diluting a weak LAC effect (56, 58). All direct oral anticoagulants (DOACs) extend dRVVT even at expected trough levels, potentially skewing LAC results. Rivaroxaban predominantly affects the screening phase more than the confirmation assay, resulting in higher dRVVT ratios and possible false positives, while apixaban has a more pronounced impact on the confirmation than the screening, leading to lower ratios and potential false negatives (59). Commercial neutralizers or antidotes, like DOACStop, might mitigate the effects of DOACs, although results should be interpreted cautiously due to possible incomplete neutralization and interference with other test components affecting clotting times (61, 62, 63, 64). Ideally, DOACs could be temporarily interrupted or switched to LMWH for LAC testing; if this is impractical, they should be tested at their lowest levels with added DOAC neutralizers while concurrently assessing drug levels to demonstrate some evidence of DOAC neutralization (57). The Textarin ratio, which utilizes snake venom as a prothrombin activator, is less influenced by anti-FXa DOACs, although its use is limited by the absence of standardized commercial assays (49).

Detection of anti-β2GP-I and ACA typically occurs through commercially available ELISA or chemiluminescent assays (65, 66). These assays quantify levels of IgG and IgM antibodies, with values exceeding the 99th percentile deemed positive (47). IgG antibodies have a stronger association with thrombosis (67). However, false positives can arise from the detection of non-specific antibodies due to factors such as infections, hypergammaglobulinemia, or the presence of rheumatoid factor (68). As with LAC tests, positive results should be repeated after 12 weeks (47).

Conclusion

Thrombophilia screening remains a contentious aspect of clinical pathology, primarily due to variations in guidelines and the interpretation of results. It is critical to recognize that not all patients with a history of venous thromboembolism (VTE) require extensive thrombophilia testing; instead,

evaluations should be grounded in clinical relevance and tailored to influence management decisions. This review highlights the importance of distinguishing between inherited and acquired thrombophilias, which can pose varying degrees of risk. The prevalence and associated relative risks of specific thrombophilias, such as factor V Leiden and prothrombin mutations, underscore the need for accurate diagnostic strategies in diverse populations. Furthermore, the discussion surrounding the pre-analytical phase of testing is vital, as factors such as specimen collection, transport conditions, and processing protocols can significantly affect the outcomes of thrombophilia assays. For instance, maintaining a platelet count below specified thresholds is crucial for achieving reliable results in functional clot-based assays. Moreover, it is essential to address the potential interferences caused by anticoagulants, acute illnesses, and hormonal treatments, which may skew test results and lead to misinterpretations. As therapeutic options for managing thrombophilia evolve, including direct oral anticoagulants, the implications of these medications on test results must be meticulously evaluated to ensure diagnostic integrity. In summary, a comprehensive understanding of the various laboratory factors influencing thrombophilia testing is indispensable. Clinicians and laboratory personnel must engage in collaborative practices to refine testing protocols and ensure that thrombophilia screening is effectively integrated into clinical pathways for managing VTE risk. This nuanced approach not only enhances the accuracy of diagnoses but ultimately leads to better patient outcomes through tailored treatment strategies.

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فحص أهبة التخثر في علم الأمراض السريرية: التوجيهات والجدل

الملخص:
خلفية :يُعتبر فحص التخثر أمرًا حيويًا في تقييم خطر الانصمام الخثاري الوريدي(VTE) ، وخاصةً لدى المرضى الذين لديهم تاريخ من .VTE توصي الإرشادات السريرية بإجراء اختبارات مستهدفة بناءً على تأثيرات الإدارة والسياق السريري، بما في ذلك عوامل مثل الجراحة، الأورام، والحالة الهرمونية.
الهدف :يقيّم هذا الاستعراض العوامل المختبرية الهامة التي تؤثر على تفسير نتائج اختبارات التخثر، مع التركيز بشكل خاص على التثفق الوراثي والمكتسب المرتبط بـ.VTE
الطرق :يناقش الاستعراض التخثرات الشائعة، بما في ذلك عاملV Leiden ، طفرات البروثرومبين، نقص بروتينC ، بروتين S، ومضاد التخثر، بالإضافة إلى الأجسام المضادة للفوسفوليبيد. يؤكد على المتغيرات ما قبل التحليل التي تؤثر على دقة التشخيص، ويصف البروتوكولات المختبرية الموصى بها لجمع العينات ومعالجتها وإجراء الاختبارات.
النتائج :تشير النتائج الرئيسية إلى أن الطفرات الوراثية والنقص في بعض البروتينات تزيد بشكل كبير من خطر VTE في مختلف السكان. تتأثر دقة الفحوصات الوظيفية بعوامل مثل التعامل مع العينات، العلاج بمضادات التجلط، ووجود مواد متداخلة.
الخاتمة :إن التفسير السليم لاختبارات التخثر أمر ضروري للإدارة الفعالة للمرضى. فهم تأثير المتغيرات المختبرية أمر حاسم لتقليل الأخطاء التشخيصية وضمان التقييم الدقيق لمخاطر التخثر.
الكلمات المفتاحية :التثفق، الانصمام الخثاري الوريدي، العوامل المختبرية، الطفرات الوراثية، دقة التشخيص.