

THINGS WE DO FOR NO REASON: INPATIENT INHERITED THROMBOPHILIA TESTING

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The “Things We Do for No Reason” (TWDFNR) series reviews practices which have become common parts of hospital care but which may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent “black and white” conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

ABSTRACT

Inherited thrombophilia refers to a genetic condition that predisposes to an increased risk of venous thromboembolism (VTE). This disorder is prevalent in approximately 7% of the population and includes mutations such as Factor V Leiden, Prothrombin 20210, Protein C deficiency, Protein S deficiency, Antithrombin deficiency and Methylene tetrahydrofolate reductase. The relative risk of VTE is 3-20 fold greater in patients with inherited thrombophilia compared with the general population. Is testing for inherited thrombophilia recommended?

The available evidence suggests that testing for inherited thrombophilia is not recommended in most clinical settings. In patients without a personal history of VTE, thrombophilia results do not change management, as there is no evidence to support thromboprophylaxis in this setting. In patients with a personal history of provoked or unprovoked VTE, inpatient testing is not indicated, as results do not influence management, testing is not cost-effective, and a positive test result may lead to unnecessary patient anxiety or may result in unnecessary involvement of consultants. Testing in hospitalized patients has even more limitations because many thrombophilia tests are inaccurate in the setting of acute VTE and/or anticoagulation.

CASE PRESENTATION

A 23-year-old man presents to the emergency room with pleuritic chest pain and new oxygen requirement of 2 liters nasal cannula. He has a history of unprovoked lower extremity deep venous thrombosis diagnosed at age 20 and completed three months of systemic anticoagulation without complications. He reports no family history of clotting disorders or venous thromboembolism (VTE) and no reversible risk factors for VTE such as prolonged immobility, recent surgery, or high-risk medications. A computed tomogram pulmonary embolism (PE) protocol shows multiple right lower lobe, segmental pulmonary emboli. Anticoagulation is initiated and the patient is admitted to the hospital. Will inpatient inherited thrombophilia testing impact management for this case?

WHY MAY INHERITED THROMBOPHILIA TESTING PROVE HELPFUL?

The annual incidence rate of a first VTE event is estimated as 117 per 100,000 individuals per year.¹ The most common presentations are symptomatic deep-vein thrombosis (DVT) of the leg (annual incidence approximately 48 per 100,000 people), or a pulmonary embolism (annual incidence approximately 69 per 100,000 people).¹ Pulmonary embolism results in death in up to 30% of untreated patients and 2.5% of patients that receive systemic anticoagulation.² Principal in the pathogenesis of VTE are factors described by Virchow's Triad: venous stasis, endothelial injury, and systemic hypercoagulability. By identifying a mutation in one or more of the factors in the clotting pathway, an evaluation for inherited thrombophilia theoretically may unearth factors that drive systemic hypercoagulability and inform decision-making so as to prevent future events.

Inherited thrombophilia refers to a genetic condition that predisposes to an increased risk of VTE.³ Approximately 7% of the general population has inherited thrombophilia, which includes Factor V Leiden mutation (FVL), Prothrombin 20210 mutation (PT20210), Protein C deficiency, Protein S deficiency, Antithrombin III (ATIII) deficiency and Methylene tetrahydrofolate reductase mutation (MTHFR).⁴ Of note, the definition does not include acquired etiologies, such as antiphospholipid antibody syndrome. Depending on the underlying condition and expression of the genetic abnormality, the relative risk of VTE in patients with inherited thrombophilia is 3-20 fold greater than that of the general population.⁵ Therefore, it is logical to consider that testing for inherited thrombophilia might be clinically useful. However, the evidence for doing so is very limited.

DOES INHERITED THROMBOPHILIA TESTING CHANGE MANAGEMENT?

An inherited thrombophilia evaluation is unlikely to affect management in most clinical settings. There is no current evidence to support primary prophylaxis⁶ nor is there evidence that management of patients with recurrent VTE should be altered in the setting of inherited thrombophilia

To date, no prospective trials have evaluated the efficacy of anticoagulant use for primary prevention of VTE in patients with inherited thrombophilia.⁶ Given the limited evidence for thromboprophylaxis and risks of anticoagulation, primary prevention for patients with inherited thrombophilia that remain asymptomatic is not recommended by the current American College of Chest Physicians (ACCP) guidelines.^{7,8}

Similarly, in patients with a first VTE or recurrent VTE, diagnosis of inherited thrombophilia is often not associated with recurrent events, which suggests that other

nongenetic factors may be just as important, if not more important, in determining the risk of recurrence.⁹ While no randomized controlled or controlled clinical trials have evaluated the effects of testing for inherited thrombophilia on recurrent VTE,^{10,11} several prospective studies have assessed risk factors for recurrence. Data from these studies suggest that recurrence rates after unprovoked VTE are only weakly correlated with inherited thrombophilia status.^{12,13} Rather, it is postulated that patients with recurrent VTE may exhibit a “prothrombotic tendency” regardless of underlying genetic predisposition. In this case, decisions regarding anticoagulation do not vary by thrombophilia status. Instead, thrombophilia testing may divert attention away from the management of more prevalent, potentially modifiable risk factors such as immobility, oral contraceptive use, or malignancy - all of which are associated with recurrent VTE.¹⁴

These provoking factors are the most important determinants of the chance of VTE recurrence as well as the most significant factors to take into account when deciding duration of anticoagulation.

Christiansen et al. performed a prospective study evaluating the association between recurrent VTE and thrombophilia status. After following 474 patients with confirmed first episode VTE for a mean of 7.3 years, no statistically significant risk of VTE was found for patients with FVL (hazard ratio [HR] 1.2, 95% CI 0.7-1.9), PT20210 (HR 0.7, 95% CI 0.3-2.0) or an anticoagulant (protein C, protein S or ATIII) deficiency (HR 1.8, 95% CI 0.9-3.7).¹⁵ Although unexplained VTE was statistically associated with VTE recurrence, heritable thrombophilia status was not.

In a systematic review and meta-analysis investigating the association of FVL and PT20210 with recurrent VTE, Ho and colleagues found a statistically significant risk of recurrent VTE in patients with inherited thrombophilia due to FVL (OR 1.41, 95% CI 1.14-1.75) and PT20210 (OR 1.72, 95% CI 1.27-2.31), “i.e., at most, only up to 1 in 6

recurrent VTEs may be attributable to these mutations".¹⁶ Based on this relatively modest effect, the authors question the utility of testing for inherited thrombophilia, as thrombophilia status is unlikely to warrant a change in type or duration of treatment.

Regardless of whether an underlying inherited thrombophilia is identified, patients with history of recurrent VTE are often candidates for long-term anticoagulation.

Testing for inherited thrombophilia in patients with prior VTE events will therefore not influence decisions regarding clinical management. Additionally, such testing may be confounded by ongoing disease or treatment (see table 1). For example, Protein C, Protein S antigen, and ATIII levels are low in the setting of acute VTE.^{17,18} Likewise, protein C and S (vitamin-K dependent proteins) will be low in the setting of anticoagulation with warfarin.¹⁹ Moreover, ATIII activity and antigen levels are low in the setting of heparin use.²⁰ Lack of provider awareness regarding these interactions may have important negative consequences, including a spurious diagnosis of thrombophilia,^{21,22} unnecessary hematology consultation, and psychological distress to patients in the form of ongoing unwarranted testing or apprehension regarding recurrence.²³

Additionally, this expensive evaluation has estimated direct costs of \$1,100 to \$2,400 per thrombophilia panel based on estimation of charges billed by large commercial laboratory.^{24,25} In 2014, over 280,000 claims were submitted under Medicare Part B across all care settings for a thrombophilia analysis including FVL, PT20210 and MTHFR gene mutations²⁴, which would equate to between \$300,000,000 to \$672,000,000.²⁶ Unfortunately, there have been no large-scale trials to assess cost-effectiveness. However, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group stated that "cost-effectiveness modeling studies in

this area require updating with current VTE risk estimates but are suggestive that routine FVL/PT testing is not cost-effective.”²⁷

ARE THERE CIRCUMSTANCES IN WHICH INPATIENT INHERITED THROMBOPHILIA TESTING PROVES BENEFICIAL?

The evidence for when to test for inherited thrombophilia is very limited and is often based on individualized risk. The current EGAPP guidelines acknowledge this limitation, specifically noting that there is a paucity of data evaluating management or prophylaxis of patients with homozygous or compound heterozygous FVL or P20210 mutation, and a lack of data surrounding whether or not knowledge of thrombophilia mutation should affect anticoagulation treatment.²⁷ This is why an individualized approach is deemed necessary. For example, the decision to prescribe hormone replacement therapy in women with a family history of inherited thrombophilia may be better informed by testing prior to treatment. Similarly, pregnant women with family history or personal history of VTE may also benefit from inherited thrombophilia testing as this may influence antepartum or post-partum management.^{28,29} The National Institute for Health and Clinical Excellence (NICE) guidelines recommend consideration of testing for hereditary thrombophilia in patients with unprovoked VTE and first degree relative with VTE, if stopping anticoagulation treatment is planned – however, these recommendations are based solely Guideline Development Group’s experience and opinion.³⁰ . Regardless, testing for inherited thrombophilia has significant potential consequences. Patients at risk should meet with an outpatient hematologist and/or a genetic counselor, if available, to determine the risks and benefits of testing.

WHAT DO GUIDELINES SAY ABOUT INHERITED THROMBOPHILIA TESTING?

The most recent NICE guidelines recommend against offering inherited thrombophilia testing to patients presenting with a provoked VTE in any clinical setting.³⁰ In patients diagnosed with unprovoked VTE, testing should not be considered unless a first degree relative with a history of VTE exists.³⁰ The NICE guidelines also recommend against routinely offering thrombophilia testing to asymptomatic first-degree relatives of patients with a history of VTE or known inherited thrombophilia. This recommendation is reflected in the American Society of Hematology's Choosing Wisely recommendations since 2013.³¹ Further, The American College of Medical Genetics and Genomics' Choosing Wisely recommendations from 2015 state that MTHFR mutations should never be included in any thrombophilia workup as "recent meta-analyses have disproven an association between the presence of these variants and venous thromboembolism."³²

The EGAPP Working Group recommends against routine testing for FVL or PT20210 in patients who present with an idiopathic VTE, as longer-term anticoagulation offers similar benefits to patients with or without these mutations.²⁷ EGAPP also recommends against testing asymptomatic adult family members of patients with VTE and/or an FVL or PT20210 mutation for the purpose of considering primary prophylactic anticoagulation. In these circumstances, it is felt that the potential risks of thrombophilia testing outweigh any potential benefits.

HOW SHOULD HOSPITALISTS APPROACH TESTING OF INHERITED THROMBOPHILIA?

The providers in our case presentation are challenged with determining whether inpatient thrombophilia evaluation will add value to the evaluation of patients with unprovoked VTE. The available evidence suggests that clinicians should avoid ordering thrombophilia testing for hospitalized patients with unprovoked VTE because (a) many thrombophilia tests are inaccurate in the setting of acute VTE and/or anticoagulation; (b)

result of testing often do not influence management, (c) testing is not cost-effective; (d) a positive test result may lead to unnecessary patient anxiety, and; (e) testing may result in inappropriately prolonged anticoagulation courses or unnecessary involvement of inpatient consultants. For these reasons, the patient in our case presentation should not be tested for inherited thrombophilia. In patients with personal or family histories of recurrent thromboembolism, modifiable clinical risk factors should be addressed, as these are more likely to influence treatment decisions compared to genetic testing. Finally, patients may be referred to an outpatient hematologist or geneticist for individualized discussions of risks and benefits of testing for inherited thrombophilia.

CONCLUSION

Inpatient evaluation for inherited thrombophilia for VTE is not clinically useful, cost-effective or reliable in the setting of VTE. The result of such testing does not affect management of acute primary or recurrent VTE. Testing should only be considered using an individualized approach in the outpatient setting with appropriate genetic counseling.

Do you think this is a low-value practice? Is this truly a “Thing We Do for No Reason?”

Let us know what you do in your practice and propose ideas for other “Things We Do for No Reason” topics. Please join in the conversation online at Twitter

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Table 1. Limitations of thrombophilia workup in setting of acute VTE or anticoagulation

	Acute VTE	Anticoagulation with warfarin	Anticoagulation with NOACs	Anticoagulation with heparin/LMWH
FVL/PT/MTHFR gene mutations	Not a limitation	Not a limitation	Not a limitation	Not a limitation
Protein C*	Decreased	Decreased	No impact	No impact
Protein S*	Decreased	Decreased	No impact	No impact
ATIII activity	Decreased	Slight increase	Slight increase	Decreased
ATIII antigen	Decreased	Slight increase	Slight increase	Decreased

LMWH = Low molecular weight heparin, NOACs = Novel oral anti-coagulants (anti-Xa or Direct thrombin inhibitors), FVL = Factor V Leiden gene mutation, PT = Prothrombin 20210 gene mutation, MTHFR = methylenetetrahydrofolate reductase gene mutation, ATIII = Antithrombin deficiency

**Deficiency in both protein and functional assays*

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