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Hypercoagulable workup in a community hospital setting: to test or not to test; that is the question

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ABSTRACT

Background: Thrombophilia tests are often ordered unnecessarily and/or inappropriately, with significant impact on healthcare costs, hospital resources, time, and potential harm to the patient.

Objective: To identify the incidence of unnecessary and inappropriate thrombophilia testing in a community hospital setting.

Methods: We retrospectively reviewed electronic medical records for patients who underwent inpatient thrombophilia testing at The Brooklyn Hospital Center from 1/1/2018 to 12/31/2018. The indications, and details of the tests, and associated costs were recorded.

Results: A total of 62 patients were included (mean age 45.8, 67.7% female). In 57/62 (91.9%) patients, tests were ordered in the acute phase of thrombosis. At the time the tests were ordered, 29/62 (46.8%) patients were on anticoagulation. Positive results were found in 21/62 (53.2%) patients, but was repeated in only 1/21 (4.7%) patient. Results for 51/62 (82%) patients were obtained after discharge. The hematology-oncology service was consulted in 5/62 (8.1%) cases and recommended testing in only 1 (1.6%) patient. Only 1 (1.6%) patient had both an appropriate indication and appropriate testing. Costs for the 273 total tests were $26,400.

Conclusion: Thrombophilia tests were often ordered inappropriately and unnecessarily. We recommend testing only for patients with inpatient status under recommendation from the hematology-oncology service.

1. Introduction

Inherited and acquired thrombophilia increases the risk of thromboembolism [1]. Determining whether a thrombophilia test is indicated and choosing the correct test from many available options is challenging. In most cases, the results of a thrombophilia test do not affect patient management [1,2].

In addition, guidelines are not uniform as to when testing is appropriate [1,3,4]. The American Society of Hematology recommends against routine ordering thrombophilia tests, especially in the setting of major transient risk factors that can skew the results [3]. As per expert opinion, thrombophilia testing for any indication other than unprovoked arterial thrombosis is unnecessary in the inpatient setting [1,5,6]. Thus, it would only be ideal to order the antiphospholipid panel in a patient with stroke when it will lead to a change in the management from antiplatelet to anticoagulation.

Moreover, testing for thrombophilia is costly, with panels ranging from $1,100 and $2,400, and annual Medicare spending between $300–$672 million in the USA on thrombophilia testing [7,8]. Institutional studies have reported annual costs of $62,000 to over $1 million for thrombophilia testing [9,10]. Shen et al

reported that consultation with transfusion medicine service prior to ordering thrombophilia tests saved $104,400 per month and reduced panels ordered by 92% [10]. These figures are likely to vary depending on the number of tests and patients.

Unnecessary testing can cause harm to patients, particularly via the use of inappropriate anticoagulant therapy which increases the risk of bleeding or can give false assurance if negative [11]. Moreover, many tests are affected by the acute phase of thrombosis and/or the presence of anticoagulation at the time of testing.

Given the costliness and potential harm to patients due to inappropriate thrombophilia testing and the lack of data from a community hospital setting, we conducted a retrospective analysis to identify the incidence and cost of these tests being performed unnecessarily and inappropriately.

2. Materials and methods

2.1. Patient selection

This was a retrospective observational single-center study performed at a community hospital. We collected

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clinical data from electronic medical records of patients over age 21 with at least one thrombophilia test ordered for hypercoagulable work up at The Brooklyn Hospital Center between January 2018 to December 2018 in the inpatient setting. Exclusion criteria included age <21 years, thrombophilia tests done as outpatients, lack of data, tests ordered for workup of connective tissues diseases, and patients who were not seen at Brooklyn Hospital. We recorded patient demographics, indications for testing, types of tests ordered, timing of ordering, results of testing, whether positive tests were repeated, whether testing was performed while the patient was on anticoagulation and/or in the acute phase of thromboses, and if the hematology-oncology service was consulted prior to ordering these tests.

This study had four major aims. First, to identify tests performed unnecessarily i.e. when not indicated. Unnecessary tests were defined as tests that were done for any indication other than unprovoked arterial thrombosis or recurrent pregnancy loss [1,5,6]. Secondly, to identify tests performed inappropriately [1,5,6]. Inappropriate tests were defined as:

(1) Use of concurrent anticoagulation during testing
(2) Testing in acute phase of thrombosis
(3) Potential for false diagnosis, if the test was not repeated after a first positive for confirmation
(4) Results that came back after discharge of the patient

Thirdly, we aimed to identify whether thrombophilia testing during the inpatient setting affected the clinical management of these patients; i.e. whether the patient was treated with anticoagulation by the time of discharge based on positive thrombophilia results. Lastly, we aimed to identify the unnecessary healthcare cost burden as a result of testing.

2.2. Statistical analysis

Descriptive statistics were used to present data and summarize the results. Continuous variables were presented using means, standard deviations, frequencies, and percentages. A Chi square test was used to compare the number of patients with inappropriate vs. appropriate indications. An *a priori* power analysis revealed that with a large effect size and in order to achieve a power of at least 0.80, the total required sample size needed to be at least 49 patients.

3. Results

Of the 62 patients with inpatient status included in the study, 42 (67.7%) were female, and the mean age was 45.8 ± 14.3. The indications for thrombophilia testing are presented in Table 1. A total of 14 (22.6%) patients had appropriate indications for thrombophilia testing;

Table 1. Indications for thrombophilia testing in the inpatient setting.

Indication (N = 62)	Frequency, n (%)
Appropriate Indications	14/62 (22.6%)
Unprovoked arterial thrombosis	10 (16.1%)
Recurrent pregnancy loss	4 (6.5%)
Inappropriate Indications	48/62 (77.4%)
Provoked arterial thrombosis	17 (27.4%)
Provoked or Unprovoked venous thrombosis	18 (29.0%)
Others*	13 (22.6%)

*Others included leg swelling with no DVT, suspected PE found to be negative, transient ischemic attack, hematuria, nephrotic proteinuria, suspected DVT found to be negative, fevers, syncope

of which 10 (16.1%) had unprovoked arterial thrombus, and 4 (6.5%) had recurrent pregnancy loss. The remaining 48 patients (77.4%) had inappropriate indications, which included provoked arterial thrombus in 17 (27.4%) patients, provoked and unprovoked venous thrombus in 18 (29.0%) patients, and other inappropriate indications in the remaining 13 (22.6%) patients. A Chi-square analysis revealed a significant difference between the 22.6% of patients with appropriate indications and the 77.4% with inappropriate indications (p < 0.001).

Testing characteristics are reported in Table 2. In 57/62 (91.9%) patients, tests were ordered in the acute phase of the thrombosis or less than 1 week of the event. In 29/62 (46.8%) patients, tests were ordered while the patient was on anticoagulation. Positive test results were found in 21/62 (53.2%) patients, but repeat testing was only done in 1/21 (4.7%) patients. Results for 51/62 (82.3%) patients came back after they were discharged. The hematology-oncology service was consulted in 5/62 (8.1%) patients and recommended testing in only 1 (1.6%) patient. A total of 273 tests were performed with an estimated expenditure of $26,400. Among all 62 patients, only 1 (1.6%) patient had an appropriate indication with appropriate testing. No change in management was observed.

Table 3 shows the thrombophilia tests ordered and their results. The most commonly ordered tests were anti-cardiolipin (aCL), ordered for 37 (59.7%) patients, anti-thrombin (AT) for 36 (58.1%), and protein C (PC) activity for 36 (58.1%) patients. Positive test results were found in 33 out of 273 total tests (12.1%). The most frequent deficiencies were found in protein S in

Table 2. Characteristics of thrombophilia testing performed.

Thrombophilia Testing	Frequency, n (%)
Acute Phase of Thrombosis[a]	57/62 (91.9%)
On anticoagulation[a]	29/62 (46.8%)
Tests positive	21/62 (33.9%)
Repeat testing (if results were positive)	1/21 (4.7%)
Results after discharge	51/62 (82.3%)
Hematology-oncology consulted	5/62 (8.1%)
Hematology-oncology recommended testing	1/5 (20.0%)
Change in management	0/62 (0.0%)

[a]note only included if the tests performed on these patients were noted to be changed by acute phase/anticoagulation

Table 3. Thrombophilia tests ordered and results.

Test	Total Tests (n)	Positive Tests (n)	Repeated Tests (n)
LA	31	5	0
aCL	37	5	1
aB2GPI	20	2	0
FVL	33	0	0
PGM	12	1	0
Prothrombin antibodies	2	0	0
PC	36	4	1
PC, total antigen	13	1	0
PS	35	10	1
PS, total antigen	14	0	0
AT	36	5	1
TOTAL	**273**	**33**	**4**

LA, lupus anticoagulant; aCL, anti-cardiolipin; aβ2GPI, anti-beta2 Glycoprotein I; aPS, anti-phosphatidylserine; aPT, anti-prothrombin; APCR, activated protein C Resistance; FVL, Factor V Leiden; PGM, Prothrombin Gene Mutation 20210A; PC, protein C activity; PS, protein S activity; AT, Antithrombin; FVIII, Factor VIII

Table 4. Thrombophilia tests.

Appropriate Tests	Affected by Anticoagulation	Affected by Acute Phase
Protein C level	Y	Y
Protein S level	Y	Y
Antithrombin	Y	Y
Lupus Anticoagulant	Y	N
Anticardiolipin antibodies	N	N
Anti-beta 2 glycoprotein antibodies	N	N
Prothrombin gene mutation	N	N
Factor V Leiden	N	N

10/35 (28.6%) tests, lupus anticoagulant (LA) in 5/31 (16.1%) tests, and AT in 5/36 (13.9%) tests.

4. Discussion

This represents one of the only retrospective studies on thrombophilia testing performed in a community hospital setting. In our study, only one patient was found to have testing done appropriately and for a necessary indication, and thus most of the $26,400 that our hospital spent on these tests was used unnecessarily. Guidelines suggest that in patients who have provoking risk factors for either venous or arterial thromboses, testing should not be ordered as it will not result in a change in management [3]. We found that the majority of tests were ordered for venous thromboses; patients with unprovoked venous thromboses need to be on anticoagulation regardless of the test results, and therefore testing is not indicated in the inpatient setting.

For patients with an unprovoked arterial thrombosis, a change in management may occur from antiplatelet to anticoagulation and testing is thus appropriate [1,5,6]. In the acute inpatient setting, it is recommended to check the anti-phospholipid panel (beta2 glycoprotein antibody, the aCL antibody, and LA (if the patient is not on anticoagulation), as these tests are not affected by acute thromboses and thus are appropriate to order [1,5,6]. For example, in a patient who developed a stroke and is not on anticoagulation and is found to be antiphospholipid antibodies positive, the management would change to anticoagulation. Whether to start such a patient on anticoagulation pending results of testing, is unclear per published guidelines.

Tests such as PC, PS, and AT-III are affected by the acute phase of thrombosis [12,13], and thus may have led to false positives in the patients who had these tests ordered in that setting which as we see from our data was the majority of patients. These three tests, along with LA, are also affected by concurrent anticoagulation (refer to Table 4) [14]. Just under half of the patients either were on anticoagulation already or they were newly started on anticoagulation prior to the ordering of these tests, which were therefore ordered inappropriately.

It should also be noted that the hypercoagulable panel consists of the following tests: PC and PS, AT-III, LA, aCL and glycoprotein antibodies, prothrombin gene mutation, and Factor V Leiden. There was a large amount of heterogeneity in the tests ordered across patients in this study, indicating that the clinicians are not clear on the appropriate tests to order and that workup was not done properly. Numerous tests were also ordered when they were not part of the hypercoagulable panel e.g. Factor V levels instead of Factor V Leiden, Protein C antigen or Protein S Antigen instead of Protein C or Protein S levels, Homocysteine levels, Prothrombin antibodies instead of prothrombin gene mutation, and B2 microglobulin instead of B2 glycoprotein.

We hypothesize that the majority of practices operate with a significantly higher percentage of thrombophilia tests ordered inappropriately. The percentage of patients with inappropriate indications for testing in this study are in agreement with several recent similar studies. Shen et al reporting appropriate indications in 34% of patients, in which appropriate testing was also defined as an unprovoked thrombosis or ≥ 3 pregnancy losses [9]. The authors established local guidelines to prevent testing during the acute thrombotic event or while the patient is on anticoagulation, resulting in an 84% reduction in ordered tests after 22 months and an estimated savings of over $100,000 per month. Mou et al published two retrospective studies performed at Stanford Hospital; in 2016, they reported a 1 year retrospective study of 889 patients tested for thrombophilia, 37.2% of which were deemed inappropriate, leading to a cumulative hospital charge of over $150,000 [15]. In 2017, the same group published a 2 year retrospective review of 1817 thrombophilia orders and found that 42.7% were potentially inappropriate, with associated costs over $40,000 [16]. Finally, Cox et al performed a retrospective analysis of 163 patients at an academic medical center in Utah, and found that 77% of patients received one or more thrombophilia test with minimal clinical utility; only 2 of their patients had a change in management after testing [17].

Although results would undoubtedly vary between institutions depending on a variety of factors including clinician experience, volume of patients with similar pathology, local guidelines, and hospital setting, these studies in combination with our results confirm that a large amount of unnecessary and wasteful testing across multiple centers in the USA, and that routine inclusion of hematology-oncology specialists and de-implementation efforts would substantially reduce costs and improve patient care.

In our study, the hematology service was only consulted in 8% of cases and recommended testing in 1 patient. Many factors should be taken into consideration prior to ordering thrombophilia tests, and experts strongly recommend to consult a hematologist for thrombophilia evaluation to avoid inappropriate or unwarranted tests [18]. In a study by Favaloro et al that investigated the incidence of positive thrombophilia testing in patients with identifiable thrombotic event or pregnancy morbidity, 51% were tested during the acute phase of the thrombus, increasing the risk of a false-positive test [11]. Additionally, 34% were on anticoagulation therapy at the time of testing, making these tests non-representative of patients' baseline coagulation responses. Indeed, that study reported a 46% confirmation rate for abnormal tests.

No change in management occurred in any of our patients due to a combination of the above factors. Prior data is consistent with our results and does not show a significant change in rate of recurrent VTE between patients who undergo testing and those who do not [1]. Approximately one third of our patients were found to have positive tests, but only 10% of those were repeated for confirmation. This may have been seen because most of the test results came back after discharge and many are sent out and the turnaround time is prolonged.

4.1. Limitations

The main limitation of this study is the retrospective, single-center design. Differentiating provoked from unprovoked thromboses required additional review of the documentation of risk factors, which was largely inconsistent and therefore the incidence of provoked thromboses may have been underestimated.

5. Conclusions

We routinely encounter situations where health care providers have ordered thrombophilia tests inappropriately, which has led to incorrect interpretation of results. Testing should only be performed if the results will be used to modify medical management or to aid in primary prevention. It is paramount to ensure necessary testing and correct assessment to avoid futile genetic counseling, loss of valuable time, unwarranted patient follow-ups, unneeded anxiety, and potentially harmful treatments. We also recommend that tests be restricted as inpatient and that a hematology-oncology service be consulted prior to ordering the tests.

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