Stanford University

HIGH VALUE CARE: OPTIMAL APPROACH TO THROMBOPHILIA WORKUPS & FRESH FROZEN PLASMA USE

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Learning Objectives

After completion of this session, the learner should be able to:

- Recognize the costs associated with thrombophilia testing and administration of fresh frozen plasma (FFP)
- Distinguish between scenarios where thrombophilia testing may or may not benefit a patient
- Identify which thrombophilias deserve more aggressive diagnostic and therapeutic management
- Contrast scenarios where FFP administration may be appropriate vs. inappropriate
- Apply a cost-benefit analysis when considering thrombophilia work-ups for future patients
- Apply a cost-benefit analysis when considering FFP administration to future patients with mild coagulopathy
Choosing Wisely is a national medical stewardship campaign led by the American Board of Internal Medicine (ABIM) Foundation.

The campaign works with approximately 50 medical professional societies from a variety of clinical specialties.

Each society is asked to identify five tests, treatments, or procedures that physicians and patients should question.

These five recommendations are based on evidence, cost, frequency, and clinical purview.
5 Recommendations by the American Society of Hematology (ASH)

1. Do not transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac, in-patients).

2. Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).

3. Don't use inferior vena cava (IVC) filters routinely in patients with acute venous thromboembolism (VTE).

4. Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).

5. Limit surveillance computed tomography (CT) scans in asymptomatic patients following curative-intent treatment for aggressive lymphoma.
The ASH recommendations certainly provide us with some “low hanging fruit” to pick.

Low hanging fruit, example #1: For a patient who is diagnosed with a DVT/PE shortly after major surgery, there is no need to send a thrombophilia work-up.

Low hanging fruit, example #2: For a patient on warfarin for atrial fibrillation who has an INR of 6 without bleeding, there is no need to give FFP.

In this hour, we want to move beyond the low hanging fruit and take a closer look at the literature and recommendations regarding thrombophilia work-ups and FFP administration.
Why Did ASH Target Thrombophilias?

“Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients are incorrectly labeled as thrombophilic.”1

“Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors.”1

Thrombophilia testing can be ordered at inappropriate times (e.g. tests for Protein C while the patient is already on warfarin)

Thrombophilia testing is expensive - at Stanford, the charge to patients for a complete thrombophilia workup is several thousand dollars

A 35 year-old female is presenting to your clinic. Her father was recently hospitalized for a DVT/PE and was found to be heterozygous for Factor V Leiden at that time. She and her siblings decided to be tested, and she was found to also be heterozygous for Factor V Leiden. She has never had a VTE. She uses condoms for birth control. How should she be managed?

A. Start ASA 81mg daily indefinitely
B. Start Warfarin indefinitely
C. Start Rivaroxaban indefinitely
D. No anticoagulation at this time
“In persons with asymptomatic thrombophilia (i.e., without a previous history of VTE), we recommend against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE.” (Grade 1C)

Factor V Leiden, the most common thrombophilia, has a prevalence of nearly 7% in the general population. It is present in up to 20% of patients with an idiopathic first-time VTE.

However, the annual incidence of a first episode of VTE in Factor V Leiden heterozygotes is very low.

In contrast, the annual incidence of major bleeding with oral anticoagulants is 2-3%.

Table 1. Risks for and Incidence of a First Episode of Venous Thrombosis

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</tr>
<tr>
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</tr>
<tr>
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<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Factor V Leiden heterozygote (7)</td>
<td>7</td>
<td>0.06</td>
</tr>
<tr>
<td>Oral contraceptive use and factor V Leiden mutation (10)</td>
<td>35</td>
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<td>Factor V Leiden homozygotes (11)</td>
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A 39 year-old female presents to your anticoagulation clinic. She has a history of an idiopathic DVT and was found to have the prothrombin G20210A mutation. She has been on warfarin for the last 6 months. She is now asymptomatic and a d-dimer performed in clinic was negative. What is your next step in management?

A. Continue warfarin for 6 more months (1 year total duration)
B. Continue warfarin indefinitely
C. Stop warfarin and transition to ASA 81mg prophylaxis
D. Stop warfarin
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Most Thrombophilia Patients Do Not Have Higher Recurrence Rates of VTE

Christiansen, S et al. JAMA. 2005;293:2352-2361

- Cohort of 497 patients with 1st time VTE
- All patients followed up to 12 years after completing warfarin (3 months duration) for primary VTE
- No significant difference in recurrence. HR 1.4 (95% CI: 0.9-2.2)
- Exclusions: age >70, cancer


- Cohort of 570 patients with 1st time VTE
- All patients followed up to 2 years after completing warfarin (6 months duration) for primary VTE
- No significant difference in recurrence. HR 1.5 (95% CI: 0.82-2.8)
- Exclusions: APLS, cancer
Most Thrombophilia Patients Do Not Have Higher Recurrence Rates of VTE

This holds true when individual thrombophilias are examined (FVL, PG20210A, Factor VIII, homocysteinemia, Protein C/S deficiency, antithrombin III deficiency)

As we will discuss later, anti-phospholipid antibody syndrome and PNH are exceptions and confer higher rates of recurrent VTE

\[1^{\text{Heit, JA. Amer J Hematol. 2012;87(S1):S63-S67}}\]
A 29 year-old female graduate student with no PMH is presenting to your clinic. She states that she has several relatives with a history of blood clots and wants to be tested for a thrombophilia. None of her relatives have been tested. She wants to start an OCP for birth control. Would you send off a workup?
“When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE.”

A positive family history of VTE does not accurately predict a thrombophilia diagnosis\(^1\) (likely because many VTEs in family members are caused by transient risk factors such as temporary immobility or surgery rather than by thrombophilias).

A positive family history for VTE has only a 20% positive predictive value for thrombophilia in the absence of any thrombophilic testing\(^2\).

In relatives who do have documented thrombophilias, a detailed genetic history may be useful to identify congenital disease.

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\(^2\)Legnani C et al. Eur Heart J. 2002;23:984-990
OCPs Worsen VTE Risk in Some Thrombophilia Patients

- OCPs alone have a similar risk of initial VTE compared to some thrombophilias alone.
- However, OCPs or pregnancy can worsen the risk of VTE in patients with thrombophilia.
- Some thrombophilias (e.g., homozygous FVL) have drastically higher rates of VTE with OCP use or pregnancy.
- Who should be tested?

Table 2: Relative Risk of Initial Venous Thromboembolism

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<td>Prothrombin G20210A mutation</td>
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FVL = factor V Leiden mutation; HRT = hormone replacement therapy; OCA = oral contraceptive agent; ATIII = antithrombin III deficiency.

Which of the following conditions, if suspected, deserves further workup in the setting of acute VTE?

A. PNH  
B. Antiphospholipid Antibody Syndrome  
C. Malignancy  
D. VTE associated with surgery  
E. Answers A, B, C  
F. None of the above

What workup can be done in the setting of acute VTE and/or if anticoagulation has already been initiated?
Acute VTE and/or anticoagulation can confound certain thrombophilia workups

Factor V Leiden and PG20210A can be diagnosed by genetic testing

A thrombophilia workup should be sent several weeks after a patient has completed anticoagulation

<table>
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<tr>
<th>Test</th>
<th>Acute VTE</th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin Antibodies</td>
<td>May be elevated</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>May be prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Protein C/S</td>
<td>Decreased</td>
<td>No Effect</td>
<td>Decreased</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor VIII level</td>
<td>Increased</td>
<td>No Effect</td>
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A 30 year old G4P0 woman is presenting to the ED with acute dyspnea. Her exam shows multiple necrotic skin lesions. Her CT is positive for multiple subsegmental PEs. She is hemodynamically stable. What is the most appropriate next step in management:

A) Start Warfarin
B) Start LMWH and begin a hypercoagulable workup
C) Start LMWH and defer a hypercoagulable workup until she has been off anticoagulation for several weeks
D) Begin a hypercoagulable workup, and decide which anticoagulant to administer based on her results
Antiphospholipid Antibody Syndrome (APLS)

Diagnosis made by the presence of 1 clinical criterion and 1 laboratory criterion

Clinical criteria include thrombosis/embolism (arterial or venous) or recurrent unexplained abortions

Laboratory criteria include any of the following

1. Lupus anticoagulant
2. Anti-cardiolipin antibody positivity
3. Glycoprotein-1 antibody positivity

These findings must be re-demonstrated again at 12 weeks

Requires prompt evaluation given the concern for catastrophic disease
APLS Has High Rates of Recurrence After Anticoagulation Cessation

Prospective cohort of 897 patients with anticardiolipin antibodies with 1st time VTE
- Patients were followed after stopping anticoagulation with warfarin for 6 months
- Increased rates of recurrent VTE and mortality were noted in the APLS group

Instances Where Lifelong Anticoagulation May Be Indicated

1. APLS with VTE (note that APLS is considered so high-risk that the INR targets for APLS are commonly higher – 2.5 to 3.5)

2. PNH

3. Any individual with a second episode of VTE, regardless if thrombophilia is present

4. Malignancy with VTE

5. Patients with life-threatening VTE or unusual idiopathic VTE locations*

*Mostly expert opinion
Now that we have had an opportunity to discuss thrombophilia work-ups in some detail, let’s transition to discussing FFP usage.
“While blood transfusions can be life-saving, they also carry risks that range from mild complications to death. Variation in clinical transfusion practices results in waste of a limited resource when unnecessary transfusions are given, and contributes to public health concerns about blood product shortages.” ¹

—The Joint Commission and AMA

“Most clinical uses of FFP are not supported by evidence…little evidence for the effectiveness of prophylactic use of FFP”²


²Stanworth, SJ et al. British J Hematol. 2004;126:139–52
Case 6

56 year old male with a PMH significant for cholangiocarcinoma presents with jaundice. Interventional radiology has been consulted to place a biliary stent. His INR is 1.7. The IR team is requesting that he receive 2 units of fresh frozen plasma (FFP) before his procedure to reduce the risk of bleeding.

What is the INR of FFP?

Would FFP administration reduce his risk of bleeding?
FFP Does Not Alter Mildly Elevated INR

At INRs ≤2, administration of FFP has minimal effects on post-transfusion INR.

FFP has an INR of roughly 1.4-1.7.

The change in INR per unit of FFP is linear. Higher baseline INRs do not equate to a greater change in INR after transfusion.

Holand, LL et al. Amer J Clin Path. 2006;126(1):133-139
MGH study of 121 patients with FFP administration. INR was tracked after transfusion

Pre-transfusion INR 1.1-1.85 with a median of 2 units of FFP given

Change in INR not dependent on number of units given or pre-transfusion INR

Only 0.8% of patients achieved normalization of INR after FFP

Abdel-Wahab, OI et al. Transfusion. 2006;46(8):1279-1285
Bleeding risk is not different between patients with normal coagulation parameters and those with minimally elevated INRs (INR ≤1.7 -2.0)\(^1,2,3,4\)

Studies include diverse procedures: cardiac surgery, angiography, central venous catheterization, needle biopsies, thoracentesis, paracentesis, tracheostomy, spinal surgery, lumbar puncture, etc.

\(^1\)Segal, JB et al. Transfusion. 2005;45:1413–25  
\(^3\)Desborough et al. Transfusion. 2012;20S–9S  
\(^4\)Tavares, M et al. Transfusion. 2011;51:754-61
Learning Objectives Re-Visited

After completion of this session, the learner should be able to:

1. Recognize the cost associated with thrombophilia testing and inappropriate administration of fresh frozen plasma (FFP)
2. Distinguish between scenarios where thrombophilia testing may or may not benefit a patient
3. Identify which thrombophilias deserve more aggressive diagnostic and therapeutic management
4. Contrast scenarios where FFP administration may be appropriate vs. inappropriate
5. Apply a cost-benefit analysis when considering thrombophilia work-ups for future patients
6. Apply a cost-benefit analysis when considering FFP administration to future patients with mild coagulopathy
Case 1

A 35 year old female with no PMH is referred to your clinic after a family member developed a DVT during pregnancy. The patient wants to be tested for thrombophilia. She is found to be a carrier of the Factor V Leiden mutation. She uses condoms for birth control. How should she be managed?

1. Start ASA 81mg daily indefinitely
2. Start Warfarin indefinitely
3. No anticoagulation at this time
4. Start rivaroxaban indefinitely
In patients with known thrombophilia (other than APLS) but without prior history of clotting, anti-coagulation prophylaxis is not recommended.
A 39 year old female presents to the ER with a new DVT. She has a history of antithrombin III deficiency. This is her 2nd DVT in 2 years. How long should she be anticoagulated for?

A. 3 months  
B. 6 months  
C. 1 year  
D. Indefinitely
All patients with a second episode of VTE should receive lifelong anticoagulation due to the high risk of recurrence (regardless of the presence of thrombophilia)
A 39 year old female is being seen in your anticoagulation clinic. She has a history of an idiopathic DVT and was found to have the prothrombin G20210A mutation. She has been on warfarin for the last 6 months. She is now asymptomatic. What is your next step in management?

A. Continue warfarin for 6 more months (1 year total duration)
B. Continue warfarin indefinitely
C. Stop warfarin and transition to ASA 81mg prophylaxis
D. Stop warfarin
With the exception of malignancy, PNH, or APLS, thrombophilia patients do not have higher rates of VTE recurrence after standard treatment for a 1st time VTE. Prolonged anticoagulation should generally be avoided.
Which of the following conditions, if suspected, deserves further workup in the setting of acute VTE?

A. PNH
B. Antiphospholipid Antibody Syndrome
C. Malignancy
D. A second recurrence of idiopathic VTE
E. Answers A, B, C
F. Answer C, D
Take Home Point #4

Certain hypercoagulable states (PNH, APLS, cancer) deserve further workup and life-long anticoagulation after VTE
A 21 year old female wants to start OCPs for menstrual regularity. Her mother is known to have heterozygous Factor V Leiden. She has no PMH and has never been tested. How would you counsel her on her risk of developing a VTE?

A. Her risk of VTE is significantly higher than the general population  
B. Her risk is not significantly greater than other patients on OCPs  
C. Her risk is dependent on whether or not she has FVL  
D. She should avoid OCPs until she has been tested for FVL
In patients with a family history of thrombophilia who are considering pregnancy, the decision to test for thrombophilia or give prophylaxis is more complex and requires a consultation with a specialist.

**Table 2** Relative Risk of Initial Venous Thromboembolism

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