Deep Vein Thrombosis and Pulmonary Embolism, an Updated Review

DR. NERVIK ROY, D.O.
INTERNAL MEDICINE, PGY-2
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Lecture Overview

- Case
- Review of Pathophysiology
- Approach
- Clinical Decision Making
- Treatment
- References
Points to Remember

- VTEs usually have an inciting event; if we can find the trigger, we can prevent further episodes.
- **Risk stratification** is useful to detect events if imaging modalities are not possible.
  - It can also aid us in our determination if the VTE event is severely life-threatening.
- VTEs without a trigger, due to underlying hypercoaguuble states require life-long anticoagulation
- Many studies out showing superiority of DOACs/NOACs
56 YO Caucasian Male comes with complaints of shortness of breath and unilateral (Left) leg pain for 4 days duration.

SOB has been progressively worsening for 4 days; “described as cannot catch his breath”

Left leg pain: patient initially noticed it 2 weeks ago as what he described as a “crampy” type of pain, located in the calf; however, it has been increased in intensity since 4-5 days ago.

SOB Exacerbated with exertion; leg pain is constant.

SOB Relief with rest; no improvement in LLE pain with NSAIDs/opoids

No chest pain, dizziness, syncope/near syncope, hemoptysis, abdominal pain.
Case Presentation, cont.

- Generally unremarkable PMH, no medicines except as needed albuterol inhaler
- Very fit and active; goes mountain biking
- Relevant history: patient recently had a mountain biking accident and suffered many broken bones and pneumothorax
  - Hospitalized for 4 days
  - Had chest tubes in place for 3 days, multiple rib fractures and lower extremity bruises
  - Decreased activity, more opioid use since accident
Relevant Physical exam findings:

HR: 101, RR 18-20, BP 130s/80s, O2 sat: 91% on RA

Gen: Well-developed/nourished, middle-aged Caucasian male, sitting upright in bed, mild CP distress

Resp: CTAB, no use of accessory muscles, normal AP diameter, no wheezes, rhonchi, rales. *Saturating 91% at rest, 88% after movement*

CV: Tachycardic rate (100s), normal rhythm; no murmurs/gallops/rubs

MSK: LLE – swelling without pitting edema, approximately 1.5x size of the RLE. Negative Homans sign. LLE is erythematous in coloration as compared to RLE.
Based off of this history, and physical what we are most worried about is:

- Venous Thromboembolism Events!
What are VTEs?
Venous thromboembolism (VTE) is an umbrella term for any venous clot. It includes deep vein thrombi (DVT) and pulmonary embolisms (PE).

DVTs are in the venous systems of the extremities
- Distal lower extremity DVT – includes the calf or peroneal veins
- Proximal lower extremity DVT – includes popliteal, femoral and iliac veins.
  - These are often more dangerous as they have high propensity to eventually travel to the pulmonary arteries
- Upper extremity DVT – includes axillary and subclavian veins

PE’s are in the pulmonary arteries and their branches

Can use the term to include superficial venous thrombosis (which can progress to DVTs) or other internal clots such as mesenteric clots or cerebral venous sinus thrombosis.
There are both Venous and Arterial types of thrombus, but these are different in composition and appearance.

- **Arterial thrombus** – typically composed of platelet aggregates (**white thrombus**).
- **Venous thrombus** – largely consists of fibrin and red blood cells (**red thrombus**).

We will be exploring the “Red Thrombi” in this discussion.
A deep vein thrombus (DVT) can “grow up” to become a pulmonary embolism (PE), but is part of the same spectrum of venous thromboembolism.

This is why we fear extremity VTE events.

But why do we fear PEs?

PE’s cause an exponential increase in pulmonary vascular resistance.

This in turn causes increased afterload in the RV.

Causes progressive RV failure which then causes LV failure.

The Left ventricle (LV) fails in sequence dropping cardiac output and thus shock and hemodynamic instability.
Virchow’s Triad

**HYPERCOAGULABLE STATE**
- Malignancy
- Pregnancy and peri-partum period
- Oestrogen therapy
- Trauma or surgery of lower extremity, hip, abdomen or pelvis
- Inflammatory bowel disease
- Nephrotic syndrome
- Sepsis
- Thrombophilia

**VASCULAR WALL INJURY**
- Trauma or surgery
- Venepuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

**CIRCULATORY STASIS**
- Atrial fibrillation
- Left ventricular dysfunction
- Immobility or paralysis
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy
Definitions/Pathophys, cont.

- **Provoked***
  - Setting of OCTs, recent surgery, abrupt inactivity, steroid use

- **Unprovoked**
  - Also consider in the category:
    - Recurrent DVT/PE
    - Provoked with minor, persistent, irreversible or multiple risk factors
How do we approach patient’s with VTE events?
Clinical Decision Making

Patients with the clinical exam findings described above and a history of one of the below risk factors:

- Surgery within 6 – 12 weeks**
- Active cancer
- Recent Trauma
- Recent hospitalization/immobility/nursing home admission
- Recent initiation of OCPs
- Excessive use of testosterone supplements
- Pregnancy
- Obesity
Risk stratification for DVT and PE

Some of our best tools in order for us to determine the likelihood that a patient has a VTE event is to use the patient’s history, Physical exam, labs, etc to formulate a probability that can guide decision making for treatment vs further testing vs continuing current management.

This is because treatment of VTEs carries its own risks and thus, careful planning and judgement must be used to determine the need for treatment.

- **Wells Score, Geneva Score, Minaiti Score** and **Charlotte rule**, of which the **Modified Wells Score** is the most widely used and accepted scoring system for DVTs

- For PEs: **PE Wells Score, Geneva score** are the most accepted
### Modified Wells Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented deep-vein thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep-vein thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

### Geneva Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 years or over</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate 75–94 beats per minute</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate 95 or more beats per minute</td>
<td>5</td>
</tr>
<tr>
<td>Pain on deep palpation of lower limb and unilateral edema</td>
<td>4</td>
</tr>
</tbody>
</table>

0–3 Points indicates low probability.  
4–10 Points indicates intermediate probability.  
11 Points or more indicates high probability.
The DVT Wells Score is most validated and most commonly used. It has primarily been validated in the outpatient setting.

BUT, it is not sufficient for the inpatient setting.

The Wells score performed only slightly better than chance for discrimination of risk for DVT in hospitalized patients.

It had a higher failure rate and a lower efficiency in the inpatient setting compared with that reported in the outpatient literature.

Therefore, the Wells score risk stratification is not sufficient to rule out DVT or influence management decisions in the inpatient setting.

Thus, we rely on Imaging to prove the presence or absence of DVT’s in the inpatient setting.
Risk Stratification for PE

- When it comes to PE's, there is a two-tiered approach in regards to risk-stratification that is recommended.
- First, Determine the Liklihood that the patient has a PE with risk factors, clinical signs/symptoms using:
  - PE Wells Score
  - the PERC rule
  - or the Geneva score.
Modified Wells criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs or symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (&gt;3 days) or surgery in last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous history of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer within the last 6 months</td>
<td>1</td>
</tr>
</tbody>
</table>


*Modified Wells criteria: <2 points = low risk for PE; 2-6 points = moderate risk for PE; >6 points = high risk for PE. Simplified Wells criteria: <4 points = PE unlikely; >4 points = PE likely.

Pulmonary Embolus Rule-out Criteria (PERC)

All answers to the questions below must be yes:

Low risk by Gestalt or other criteria?

- Age <50
- Pulse <100
- Oxygen saturations on room air >94%
- No unilateral leg swelling
- No Hemothysis
- No recent trauma or surgery
- No previous VTE
- No oral hormone use

Wells Criteria (For PE)  

PERC Rule
It is important to know that once a patient has been diagnosed with a PE, we must decide whether the patient has a potentially life-threatening PE. This can be found in PE's causing "right-heart strain". Can test for RHS using troponins, pro-BNPs, Echocardiograms (TTE). Trops and BNPs can be very sensitive. Thus, we must Risk stratify by PESI scoring and/or Hestia criteria to determine disposition.
## Risk stratification of PE, cont.

### PESI score

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years</td>
</tr>
<tr>
<td>Male sex</td>
<td>+ 10</td>
</tr>
<tr>
<td>Cancer</td>
<td>+ 30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+ 10</td>
</tr>
<tr>
<td>COPD</td>
<td>+ 10</td>
</tr>
<tr>
<td>HR ≥ 110 b.p.m</td>
<td>+ 20</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>+ 30</td>
</tr>
<tr>
<td>RR &gt; 30 breath per minute</td>
<td>+ 20</td>
</tr>
<tr>
<td>BT &lt; 36 °C</td>
<td>+ 20</td>
</tr>
<tr>
<td>Delirium</td>
<td>+ 60</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%</td>
<td>+ 20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Low risk**  
  - (≤ 65 class I, 66-85, class II)  
  - Mortality 1.9%

- **Intermediate risk**  
  - 86-105 class III, 106-125 class IV)  
  - Mortality 18.4%

- **High risk**  
  - (> 125 class V)  
  - Mortality 25%

### Hestia Criteria

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient hemodynamically unstable?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is thrombolysis or embolectomy necessary?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding or high risk for bleeding?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 24 hours of oxygen supply to maintain oxygen saturation &gt;90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is pulmonary embolism diagnosed during anticoagulant treatment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe pain needing intravenous pain medication for more than 24 hours?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical or social reason for treatment in the hospital for more than 24 hours? (Infection, malignancy, no support system)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does the patient have a creatinine clearance of less than 30 mL/min?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the patient have severe liver impairment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the patient pregnant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the patient have a documented history of heparin induced thrombocytopenia?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If one of the questions is answered with **YES**, the patient **can not be treated at home** in the Hestia study.
The PESI score

- Somewhat complex scoring system
- In general, with the PESI score:
  - The patient is High-Risk if hypotension present.
  - Low if minimal symptoms, and lack of RV strain on imaging.
  - Intermediate is where the waters get murkey
  - Intermediate-low if less severe RV dysfunction and patient looks well.
  - Intermediate-high if more severe RV strain, increase RV:LV diameter, patient “looks ill”, high clot burden
The PESI score has a large range of numbers, thus a Simplified PESI score can be used and is more helpful because:

- Fewer patients were classified as low risk by sPESI than PESI.
- And the sPESI derivation cohort had patients with more comorbidities than the original.

sPESI: age >80; h/o cancer, CHF, chronic lung disease; HR >110 bpm; systolic BP <100 mmHg; SaO2 <90%.

Zero = low risk. One or above = high risk.
Simplified PESI score (sPESI), cont.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>≤80</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>+1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>+1</td>
</tr>
<tr>
<td>History of chronic cardiopulmonary disease</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>&lt;110</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥110</td>
<td>+1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>≥100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>+1</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>≥90%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;90%</td>
<td>+1</td>
</tr>
</tbody>
</table>
Diagnosis?
Diagnostic tools

- **DVT:**
  - Venous US extremity with Doppler
  - D-Dimer
    - Negative D-Dimer can Rule Out DVT

- **PE:**
  - V/Q scan
  - CT-Angio Chest
  - D-Dimer
For PE, can also obtain:

- EKG
  - Tachycardia
  - Demonstration of RHS: S1Q3T3; RBBB; RAD; RAE, etc
- Transthoracic Echocardiogram
  - Demonstrating RV wall hypokinesis, dilatation, RV systolic dysfunction
- ABG
- Chest X-Ray
Treatment Algorithm for DVT

M. Streiff, 2016
Treatment Algorithm for PE

M. Streiff, 2016
How do we Treat VTEs?
Once you have properly identified the risk of the patient, we can then determine the therapy modality.

**Treatment of low or intermediate-low risk patients:** Anticoagulation with parenteral agent, vitamin K antagonist with a parenteral anticoagulant bridge, or a direct acting oral anticoagulant (DOAC).

**Treatment of intermediate-high risk patients:** Consider IV unfractionated heparin for easy on/off since these patients might need more advanced therapy if they become unstable or their symptoms fail to improve on anticoagulation.

**Treatment of high risk PE** requires Advanced therapies for PE such as Systemic thrombolytics, catheter-directed thrombolytics, thrombectomy (either surgical or catheter directed) along with IV unfractionated heparin.
Gold standard treatment for VTE is anticoagulation.

The majority of VTE can be treated with DOACs – Direct oral anticoagulant (Formerly known as “NOACs” or “novel oral anticoagulants.”)

If for some reason a patient cannot tolerate a DOAC, Warfarin can be used

- Target INR 2.5 (between 2.0-3.0)

If the patient is inpatient: Use heparin (or LMWH) if there is concern for clinical deterioration (an intermediate to high risk Submassive PE)*

- For patients with known diagnosis of Cancer, can use Lovenox; use of N/DOAC is still being studied.***
Treatment, cont.

- DOAC – Direct oral anticoagulant (Formerly known as “NOACs” or “novel oral anticoagulants.”)
  - rivaroxaban
  - apixaban
  - edoxaban
  - dabigatran
DOACs (rivaroxaban, apixaban) are used for VTE if no concern for clinical deterioration. This includes the cancer patient population even with active chemotherapy. Providers should be more wary with upper GI cancer due to increased bleeding rates. If a patient’s BMI is greater than 40, there is a reduced peak of DOACs. Blood volume goes up with body weight. Pending further evidence in patients at the extremes of weight (e.g., <50 kg, >120 kg or BMI ≥ 35 kg/m²) it is advisable to limit DOAC use to situations where vitamin K antagonists cannot be used."
Another treatment modality is catheter-directed Thrombectomy and/or Thrombolysis

- Reserved for extensive, large, massive or certain submassive VTEs causing hemodynamic instability (as discussed earlier)
- Include Systemic TPA (alteplase), IR or interventional cardiology directed thrombectomy/thrombolysis
- In these cases, consider IV unfractionated heparin if there is doubt with obtaining thrombectomy or thrombolysis
Treatment, cont.

- IVC filters have been shown to decrease pulmonary embolism in some cases but increase DVTs **
  - Isn’t helpful as prophylaxis in massive trauma patients, either***
  - Use of these devices should be limited to patients with acute VTE who cannot receive anticoagulation.
  - When IVCF are inserted for other indications this should be after much thought and coupled with appropriate documentation.
Treatment, cont.

- **Duration**
  - Provoked: at least 3 months, duration can last for up to 12 months*
  - Unprovoked: Life-long anticoagulation, along with Aspirin
    - DOAC's and Warfarin (target INR 2.5)
    - For female patients with first unprovoked VTE that want to discontinue anticoagulation, they can be risk stratified using the HERDOO2 calculator.

- There are tools to risk stratify for duration of anticoagulation as well, but they are not well validated and further testing/revisions are still occurring
If a patient has recurrent DVTs and the history does not point to a trigger, there may be an underlying hypercoaguability. Such as:

- Cancer
- APL syndrome
- Activated Protein C resistance (Factor V Leiden) or Protein C Deficiency
- Protein S Deficiency
- Elevated Factor VIII
- Sticky Platelet syndrome*

These patients will need LIFE-LONG anticoagulation.

Studies have shown however, that with DOAC’s, there is more recurrence of VTE events as compared to Warfarin**

Thus, these patients must be on Warfarin with Target INR 2.5
For inpatient...

For our patients that are inpatient and have high-risk PE’s or are hemodynamically unstable and we want to eventually have a disposition plan, we must make sure that:

- Patient is off supplemental oxygen or are at baseline oxygen requirement (COPD on Home O2)
- HR and BP are stable.
- Symptoms have improved and patient can tolerate ambulation.
- Patients must be strongly encouraged to have consistent and regular follow-up with PCP/HC provider.
When using DOACs, it is imperative that a comprehensive medication reconciliation is performed.

This is due to drug interactions with:

- Azoles
- Rifampin
- Chemotherapy agents
Back to the initial case:

- 56 YO Caucasian Male comes with complaints of shortness of breath and unilateral (Left) leg pain for 4 days duration; found to have LLE DVT as well as small, Bilateral PE’s.

- Patient was seen in the ED, started on IV Heparin.

- Patient’s symptoms were stable, O2 saturation at >95%, BP stable.

- After overnight stay, patient was discharged with Oral Anticoagulation using a DOAC (Apixaban).

- Followed up with myself after 2 weeks, doing well.

- Will keep patient on DOAC for approximately 4-5 months due to the patient having many work-travel plans; follow-up to determine if it is appropriate to discontinue.


17. https://www.stoptheclot.org

18. MDCalc.com

19. UpToDate.com
Thank you, NOMA!