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DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM:

Natural History
Rate: 0.5-1/1000
>90% patients with fatal PE die in first hour
Without anticoagulation older data suggests 40-50% of PE patients and 10% of DVT patients will die

Diagnostic Tests for Pulmonary Embolism and Deep Venous Thrombosis
Clinical symptoms: dyspnea, syncope (10%), hemoptysis (1/3), chest pain hours to days after infarction
Signs: tachypenia (70-90), tachycardia (30%),
CXR: normal in only 30% - infiltrate in 50-70% and effusion in 30%
Blood gas: 15% of patients with have pO_2 > 90 mmHg and 20% have normal Aa gradients.

Predictions Rules: Very useful in helping to diagnosis DVT/PE. One DVT and two PE prediction rules are in tables at back of handout. For PE increasing use of PERC rule to establish if patient needs evaluated.

D-Dimers: Detect breakdown products of fibrin clot. Concept is that if D-dimer is below certain level, chance of patient having thrombosis is VERY low. Specificity is low so patients with positive D-dimers need further evaluation for PE/DVT.
Latex agglutinin D-dimer: used to diagnosis DIC and **NOT** DVT/PE.
"Point of Care" (POC) rapid test: Fast and simple to use but less sensitive (80-90%). Clinically proven useful when used with clinical rules. Example: SimpleRed, Simplify
"High sensitivity D-Dimer": Almost 100% sensitive but requires special equipment. Systems extensively evaluation in literature: Vidas, Liatest. For patients over 50 can adjust for age (upper limit is age x 10ug/l or age/100g/ml)

CT Angiogram: Currently the standard test for PE. A high quality negative CT angiogram essentially rules out PE. 5-10% inadequate studies (higher in inpatients). Drawback is higher incidence of subsegmental PE and radiation exposure

V/Q Scans: Fading from use. Diagnostic only if normal or "high-probability" scan in patients with high pretest probability of PE and no pre-existing cardiac or pulmonary disease.

Pulmonary Angiogram: Standard for patients with non-diagnostic tests. Can be avoided in most patients by using combinations of other tests.

Duplex Ultrasound: Very sensitive for DVT. Can miss pelvic vein or IVC thrombosis.

Diagnostic Approach:
DVT: First assess clinical probability - if high probability then proceed to scan. If not high probability obtain high-sensitive D-dimer – if negative halt work-up. If positive then proceed to scan.

PE: Perform PERC rule – if positive then assess clinical probability of PE. If high probability consider giving first dose of anticoagulation while diagnostic work-up is being performed and proceed immediately to CT angiogram. If not high probability then obtain D-dimer. If negative stop, if positive obtain CT angiogram. If patient is pregnant or has renal insufficiency scan the legs first since a positive scan established the need for therapy.

Therapy:

Thrombolytic Therapy
DVT: IV therapy not useful. Catheter directed therapy may be useful for very symptomatic common femoral or iliac thrombosis. Since many of these patients have underlying venous lesions such as May-Thurner syndrome, venoplasty or venous stenting can be done with the lytic therapy.

PE: Consider only in the patient with refractory hypotension. Current data does NOT support use in patients with right heart dysfunction but no hypotension.

Surgical or catheter directed embolectomy: consider in patient with proven PE and refractory hypotension.

Inferior Vena Cava Filters: prevents most but not all PE. Since most indications are short-term consider use of retrievable filter. Will increase risk of future DVT.
Uses:

- Prevention of PE in patient who has proximal DVT but cannot be anticoagulated.

Key is to still anticoagulate the patient as soon as it is feasible to do so. Can remove filter with patient anticoagulated

Compression Stockings: Knee-high stockings 30-40 mmHg compression does not prevent post-phlebitic syndrome but may help pain in some patients.

Best rest: Shown in multiple clinical trials **NOT** to be useful. Patients with PE/DVT should be encouraged to ambulate as this has been shown to decrease symptoms.

In or Outpatient Therapy: Multiple clinical trials have shown that patients with DVT/PE can be treated as an outpatient **UNLESS**:

1) Patients who need to be hospitalized for other reasons than there DVT/PE such as MI etc...
2) Patients with active bleeding or considered to be at high risk for bleeding.
3) Patients who are hemodynamic instability or a requirement for oxygen therapy to maintain normal oxygen saturation.
4) Patients with contraindications to heparin.

Another risk stratification tool is the Pulmonary Embolism Severity Index

Predictors	Points Assigned
Demographics	
Age in years	Age in years
Male sex	+10
Comorbid Conditions	
Cancer	+30
Heart Failure	+10
Chronic Lung Disease	+10
Clinical Findings	
Pulse ≥ 100	+20
Systolic Blood Pressure < 100 mmHg	+30
Respiratory rare ≥ 30	+20
Temperature < 36 C	+20
Altered mental status	+60
O_2 saturation < 90%	+20

PESI Score	Class	Risk	30 day Mortality range
≤65	I	Low	0-1.1
66-85	II	Low	0-3.1
86-105	III	High	0-6.5
106-125	IV	High	3.4-10.4
➢ 125	V	High	9.2-24.5

(Arch IM 170:1383, 2010, J Thom Haem 8:1509, 2010, 8:517, 2010)

Antithrombotic Therapy

Direct Oral Anticoagulants
All shown safe and effective in DVT/PE - Xa inhibitors safer than LMWH/Warfarin

Apixaban - 10mg bid x 7 days then 5mg bid
Dabigatran - heparin for 5 days then 150mg bid
Edoxaban - heparin for 5 days then 60mg/day
Rivaroxaban - 15 mg bid x 21 days then 20mg/day

DOAC Renal Dosing:
Apixaban (25% renal clearance): VTE: increasing data can be use in dialysis patients
Dabigatran (80%): If CrCl 15-30 75 mg bid (most recommend alternative agent if CrCl < 50)
Edoxaban (50%): Approved for patients with CrCl < 95 ; 30mg/day if weight < 60kg, CrCl 15-50
Rivaroxaban (33%): VTE: CrCl < 30 do not use.

Heparin
LMWH has been shown to be as effective if not more effective for all venous thrombosis ranging from sub-massive PE to superficial DVT.

LMWH Dosing:
Enoxaparin 1mg/kg/12 hours (1.5mg/kg/24 hours for low risk patients)
Fondaparinux: 7.5 mg/day (if < 50kg: 5mg/day, if > 100 kg: 10 mg/day)
- Contraindicated in renal disease
- Limited Pregnancy data

LMWH Monitoring: most patients do not need monitoring for routine therapy. Therapeutic range best established for enoxaparin - 0.7-1.1 anti-Xa units performed **FOUR** hours after injection.

LMWH Adjustments for special patients:
Obesity: no adjustment or capping of dose for weight. Check level after third dose.
Renal disease: Clearance 10-30: 0.65mg/kg/12 hours, < 10: 1mg/kg/24 hours. Check level after third dose.
Pregnancy: LMWH has been established to be both effective and safer in pregnancy than standard heparin. Dose for body weight and check levels after third dose then every month. Can use LMWH or warfarin with breast feeding.

Warfarin: start evening of PE/DVT diagnosis. Most patients start with two doses of 5 mg/day. In younger patients (<40) consider 10 mg and in the very old (>75) use 2.5mg. All patients should receive at least **FIVE** days of heparin. Consider long term LMWH in cancer patients.

Reversal of Anticoagulation
LMWH – Protamine effective. Time after dose 0-4 hours: 1 mg protamine/1mg of enoxaparin or 100units other LMWH and repeat with 50% dose in 4 hours. Time 4-8 hours 0.5 mg of protamine/ 1mg of enoxaparin or 100 units other LMWH

Fondaparinux: Protamine NOT effective. If life threatening bleeding is present use rVIIa.

Direct oral anticoagulants - no difference in bleeding outcomes when compared to warfarin.
Dabigatran: Idarucizumab 5gm, Xa inhibitors: PCC 50 units/kg

Warfarin: PO vitamin K effective within 6-24 hours. IV rapid (4-6 hours) but most be given over 1 hour. Sub-q or IM **NOT** recommended due to erratic onset of action.

Not Bleeding: Goal to get INR back in therapeutic range
INR 4.5-10: 1 mg po vitamin K
INR > 10 2.5 mg po vitamin K

Bleeding: Goal to reverse INR (short term risk of bleeding >>risk of thrombosis)
INR 2-4.5: 1-2.5 mg vitamin K ± 15 ml/kg of FFP
INR 4.5 - 10: 2.5 - 5 mg vitamin K ± 15 ml/kg of FFP
INR > 10: 5 - 10 mg of vitamin K ± 15 ml/kg of FFP

Intracranial hemorrhage:
4-factor PCC
If INR 2-4: 25 units/kg (not to exceed 2500 units)
If INR 4-6: 35 units/kg (not to exceed 3500 units)
If INR > 6: 50 units/kg (not to exceed 5000 units)

Duration of Therapy
Superficial Venous Thrombosis: most respond to NSAID/heat. Data does show that at least a 10-12 day course (up to 42 days) of prophylactic LMWH or fondaparinux is more effective that NSAIDs and should be considered in patients with extensive (> 5cm), greater saphenous, or painful SVT. For patients who cannot afford or do not want injecton, rivaroxaban 10mg is another option

Upper Extremity DVT:
Catheter related: In PICC deep venous thrombosis hold anticoagulation unless very symptomatic and then for a month. Removal of PICC is key to resolution of thrombosis. For tunneled catheters consider removal and 1-3 months therapy. If catheter is not removed then needs 3 months of therapy.
Spontaneous: 3 months of therapy. Consider catheter directed thrombolytic therapy for extensive thrombosis especially if in a dominant arm or a young patient - both for symptom relief and to find any anatomical lesions (~75% of patients)

Muscular Calf Vein (soleus or gastrocnemius) Thrombosis: 10 days of therapeutic LMWH or direct oral anticoagulants. For patient at risk of bleeding repeat doppler in one week.

Calf Vein Thrombosis: 6 weeks of therapy. For low risk no therapy and repeat doppler in one week for progression. Low risk: provoked, < 5cm, negative D-dimer, no cancer, no history of VTE, and outpatient

Proximal Vein Thrombosis (popliteal vein and above)/PE: Duration of therapy influenced by number of thrombosis and if provoked.

Provoked first DVT or PE: 3 months. Provoking factors: trauma, surgery, bedrest > 72 hours, pregnancy, estrogen, long (> 4 hours) plane flights.

Idiopathic first DVT or PE: Strongly consider indefinite therapy direct oral anticoagulants or with warfarin INR 2-3. High risk (25% at 5 years) of recurrence in next 2 years without anticoagulation.

Two or more lower extremity proximal DVT or PE: Indefinite anticoagulation

Prevention of post-thrombotic syndrome: exercise encouraged, compression stockings only if they provide symptomatic relief.

"Incidental PE": treat same as symptomatic PE

Subsegmental PE: no treatment option if low risk: no cancer, good cardiopulmonary status, no history of VTE, no DVT, minimal symptoms, and outpatient.

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Pregnancy: LMWH has been established to be both effective and safer in pregnancy than standard heparin. Dose for body weight and check levels after third dose then every month. Can use LMWH or warfarin with breast feeding. Duration – entire course of pregnancy and at least 6 weeks after delivery – total should be at least three months.

Thrombophilia

Inherited hypercoagulable states – raises risk of first DVT but not a predictor of recurrence. NO value in checking in provoked thrombosis.

Cancer Use of LMWH for 6 month should be considered especially if lung cancer or pancreatic cancer. Can use DOAC if unable/unwilling to use LMWH. Long term LMWH is mandatory for warfarin failures. Studies have shown that incidentally discovered PE in cancer patients have the same adverse outcome as symptomatic PE and require aggressive therapy.

Visceral Vein Thrombosis: Portal vein thrombosis - unless discovered incidentally while screening cirrhotics for hepatomas all require anticoagulation. If provoked by surgery or infections 3 months otherwise indefinite. Consider JAK2/PNH screening in idiopathic cases. Budd-Chair - indefinite anticoagulation and JAK2/PNH screening.

DVT Prophylaxis:

Risk Assessment:

Low-Risk Patients

- Fully mobile medicine patients
- Procedures lasting less than 30 minutes

Medium Risk Patients

- Most medical or general, urological, or surgical patients

High Risk Patients

- Previous history of venous thrombosis (or strong family history)
- Pelvic or abdominal surgery for malignancy.
- Lower limb orthopedic surgery
- Trauma patients
- Surgery in patients with other risk factors-previous pulmonary embolism, CHF, cancer

Recommendations:

Low-Risk Patients

- Early Ambulation

Medium Risk Patients

- Standard Heparin 5000 TID or
- LMWH or
- Intermittent Pneumatic Compression Stocks (IPC) if high risk of bleeding

High Risk Patients

- Apixaban 2.5 mg bid
- Enoxaparin 40mg/day
- Fondaparinux 2.5 mg/day
- Rivaroxaban 10mg/day
- Warfarin INR 2-3

Special Situations:
Neurosurgery: non-malignant: IPC
Malignant: IPC plus LMWH

High risk Medical or ICU: LMWH

DVT predication Rule:

Variable	Points
Active Cancer	+1
Paralysis or recent plaster immobilization of lower extremity	+1
Recently bedridden for > 3 days or major surgery within 4 weeks	+1
Local tenderness	+1
Calf Swelling greater than 3cm than asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema in symptomatic leg	+1
Dilated superficial veins (non-varicose) in symptomatic leg only	+1
Alternative diagnoses as or more likely than DVT	-2

Low probability <0, Moderate probability 1-2 and high probability >3

PERC Rule

Eight questions:

1) Age < 50 years
2) Heart rate less than 100 beats per minute
3) Room air oxygen saturations 95% or greater
4) No prior deep dvt or PE
5) No recent trauma or surgery in the past 4 weeks
6) No hemoptysis
7) No exogenous estrogen
8) No clinical signs suggestive of DVT such as unilateral leg swelling

In a population with low risk for PE, patients who answer "no" to all 8 have a low (~1%) risk of PE

Clinical Probability Score for Pulmonary Embolism (1)

Variable	Points
Clinical signs and symptoms of DVT	+3
Pe as likely or more likely than alternative diagnosis	+3
Immobilization or surgery in past four weeks	1.5
Previous PE or DVT	1.5
Heart rate more than 100/min	1.5
Hemoptysis	1
Active Cancer	1

Low probability <2, moderate probability 2-6 and high probability > 6
Wells Ann Int Med 135: 108, 2001

Clinical Probability Score for Pulmonary Embolism (2)

Variable	Points
Previous DVT or PE	+2
Heart rate > 100	+1
Recent Surgery	+3
Age:	
60-79	+1
>80	+2
$PaCO_2$	
< 36 mmHg	+2
36-40 mmHg	+1
$P0_2$	
<50 mmHg	+4
50-59 mmHg	+3
60-69 mmHg	+2
70-79 mmHg	+1
Atelectasis	+1
Elevated Hemi-diaphragm	+1

Low Probability 0-4, Intermediate probability 5-8, High >9

Nomograms for Warfarin Loading

Ma Crowther, L Harrison and J Hirsh Annals of Internal Medicine 127:333, 1997

5 Mg Warfarin Nonomgram

Day	INR	Dosage (Mg)
1		5.0
2	< 1.5	5.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0

10 mg warfarin nonomgram

Day	INR	Dosage (Mg)
1		10.0
2	< 1.5	7.5-10.0
	1.5-1.9	2.5
	2.0-2.5	1.0-2.5
	>2.5	0.0
3	<1.5	5.0-10.0
	1.5-1.9	2.5-5.0
	2.0-2.5	0.0-2.5
	2.5-3.0	0.0-2.5
	>3.0	0.0
4	<1.5	10.0
	1.5-1.9	5.0-7.5
	2.0-3.0	0.0-0.5
	>3.0	0.0
5	<1.5	10.0
	1.5-1.9	7.5-10.0
	2.0-3.0	0.0-5.0
	>3.0	0.0
6	<1.5	7.5-12.5
	1.5-1.9	5.0-10.0
	2.0-3.0	0.0-7.5
	>3.0	0.0

Maintenance Warfarin Adjustment Nonomgram
(*Hatheway and Goodnight*)

INR	Dose Change
1.1-1.4	Day 1: Add 10-20% Twd* Weekly: Increase TWD by 10-20% Return: 1 Week
1.5-1.9	Day 1: Add 5-10% of TWD Weekly: Increase Twd by 5-10% Return: 2 Weeks
2.0-3.0	No Change Return: 4 Weeks
3.1-3.9	Day 1: Subtract 5-10% TWD Weekly: Reduce TWD by 10-20% Return: 2 Weeks
4.0-5.0	Day 1: No Warfarin Weekly: Reduce TWD by 10-20% Return: 1 Week
> 5.0	Stop Warfarin until INR <3.0 Decreased TWD by 20-50% Return Daily

*TWD = Total Weekly Dose

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