Family Medicine 07: 53-year-old male with leg swelling

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Learning Objectives

The student should be able to:

- Discuss the differential diagnosis of unilateral leg swelling.
- Differentiate between deep venous thrombosis, leg ulcer, and peripheral artery disease.
- Describe the impact of obesity on health.
- Describe the implications, diagnosis, and management of deep venous thrombosis.
- Discuss the value of a team-based approach to chronic disease management.

Knowledge

U.S. Mortality Due to Smoking, Hypertension, Diabetes, and Obesity

Deaths caused by smoking

Smoking is the single greatest preventable cause of death in the U.S.

From 2005–2009 approximately 480,000 people in the United States annually died prematurely from cigarette smoking or exposure to secondhand smoke.

This figure has grown from an average annual estimate of approximately 443,000 deaths from 2000–2004, but this increase is predominantly due to population growth. Although deaths from cigarette smoking have not increased significantly, they remain high. Among adults, 160,848 (41%) of deaths were attributed to cancer, 128,497 (32.7%) to cardiovascular diseases, and 103,338 (26.3%) to respiratory diseases.

The three leading specific causes of smoking-attributable death were lung cancer at 127,200, ischemic heart disease at 124,800, and chronic obstructive pulmonary disease (COPD) at 100,600. An estimated 41,284 lung cancer and heart disease deaths annually were attributable to exposure to secondhand smoke. Smoking resulted in an estimated annual average of 278,500 deaths among males and 202,000 among females in the United States.

Deaths caused by hypertension

Hypertension is the single largest risk factor for *cardiovascular* mortality in the US. Overall uncontrolled hypertension decreases life expectancy by 20 years. Most of these deaths are due to the increased risk that hypertension incurs for coronary artery disease, hypertensive cardiomyopathy, cerebrovascular disease and chronic renal disease.

Deaths caused by diabetes

Deaths caused by diabetes in the U.S.: 213,062. The majority of deaths from diabetes also results primarily from the increase in cardiovascular disease and chronic renal failure. Diabetics have twice the mortality of non-diabetics. The risk of cardiovascular disease in diabetics is so high that it is assumed that they have cardiovascular disease if they have diabetes.

Deaths caused by obesity

Deaths caused by obesity in the US: 300,000. Obesity is rapidly gaining on smoking as the single greatest cause of mortality in our country. A body mass index (BMI) of over 32 kg/m^2 has been associated with a doubled mortality rate among women over a 16-year period and obesity is estimated to cause an excess 111,909 to 365,000 death per year in the United States. Obesity on average reduces life expectancy by six to seven years. A BMI of 30–35 reduces life expectancy by two to four years while severe obesity BMI > 40 reduces life expectancy by 20 years for men and 5 years for women.

Prevention of Embolism

More than 95% of pulmonary emboli arise from thrombi in the deep venous system of the lower extremities. Ninety percent of deaths due to pulmonary embolism result within an hour or two—before diagnostic and therapeutic plans can be implemented. Therefore, prevention and prompt treatment of DVT is the most effective approach to prevent embolism and death due to PE.

Pharmacology and Management of the Vitamin K Antagonists

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The half-life of warfarin is around 40 hours, that means it will take five to seven days for the steady state to be stable. When making a dose adjustment for an outpatient on warfarin, one should wait at least this long before rechecking an INR, as checking sooner can lead to overreactions and great swings in a patient's INR. If the goal INR is substantially overshot, it increases the risk

of bleeding complications significantly.

Clinical Skills

Ulcer Classification: The Wagner Grading System

The Wagner Grading System

1. Grade 1: Diabetic ulcer (superficial)
2. Grade 2: Ulcer extension (involving ligament, tendon, joint capsule or fascia)
3. Grade 3: Deep ulcer with abscess or osteomyelitis
4. Grade 4: Gangrene forefoot (partial)
5. Grade 5: Extensive gangrene of foot

Images for the corresponding ulcer classifications.

Family Physicians Coordinate Comprehensive Multidisciplinary Care

Family medicine physicians play an essential role in optimizing patient care by coordinating comprehensive multidisciplinary care.

Management

Ulcer Management

- **Grade 1 and 2** ulcer management generally can be done as outpatient and should include extensive debridement, local wound care, and relief of pressure. If there is significant erythema and/or purulent exudate, then treatment for infection is warranted.
- **Grade 3** lesions require evaluation for possible osteomyelitis as well as peripheral artery disease. Both of these conditions may need to be addressed prior to resolution of the ulcer. Typically at least a brief hospitalization is required to address these issues.
- **Grade 4 and Grade 5** lesions require emergent hospitalization and surgical consultation, often resulting in amputation.

Requirement for Treating DVT on Outpatient Basis

In order to treat DVT on an outpatient basis:

The patient must be:

- Hemodynamically stable
- With good kidney function
- At low risk for bleeding

The home environment must be:

- Stable and supportive
- Capable of providing the patient with daily access to INR monitoring (if using warfarin as the anticoagulant)

Goals of DVT Therapy

1. Immediate inhibition of the growth of thromboemboli
2. Promotion of thromboembolic resolution
3. Prevention of recurrence

Heparin achieves the first goal, it encourages the second by allowing fibrinolytic dissolution to be achieved unopposed. It is available in two forms: unfractionated heparin or low-molecular weight heparin (LMWH).

DVT Therapy: Advantages of Low-Molecular Weight Heparin (LMWH) over Unfractionated Heparin

LMWH has several advantages over unfractionated heparin:

- Longer biologic half-life so it can be administered subcutaneously once or twice daily
- Laboratory monitoring is not required
- Dosing is fixed
- Evidence from meta-analyses suggest that LMWH is associated with fewer major bleeding complications than unfractionated heparin
- Bleeding complications are less common

LMWH may be used in the outpatient setting; whereas unfractionated heparin requires hospitalization as it is administered intravenously with the dosage based on body weight and titrated based on the activated partial thromboplastin time. One

advantage of unfractionated heparin is that it can be immediately shut off and reversed in the case of bleeding due to its very short half-life. In a patient with a significant bleeding risk (e.g. recent admission for gastrointestinal bleeding), it is advisable to choose unfractionated heparin over low molecular weight heparin, which has a much longer half-life once injected.

DVT Treatment After Initial Stabilization

Warfarin

Prothrombopenic drugs like warfarin are not suitable for initial therapy in thromboembolism because their onset of action is too slow. Their only role is in maintaining anticoagulant protection for prolonged periods.

Monitor warfarin dose by measuring the INR and titrate the warfarin dose every three to seven days to an INR of 2.0–3.0. The advantages of warfarin include its minimal cost and familiarity among medical providers. Its disadvantages include its highly variable dosing range, its requirement of frequent laboratory monitoring, and its high rate of interactions with other medications.

Factor Xa inhibitors

This relatively new class of drugs has the advantage of not requiring weekly lab monitoring of INR and thus makes adherence an easier process. Fondaparinux is the parental form of the drug and could be used instead of LMWH. Rivaroxaban and apixaban are oral factor Xa inhibitors which may be used in place of warfarin. Although these drugs have been found to be as effective as and generally safer (i.e. fewer bleeding complications) than warfarin and LMWH, the negatives of this class of medications include high cost and difficulty in reversing the anticoagulation in the face of a bleed.

Direct thrombin inhibitors

Dabigatran and edoxaban are the only direct thrombin inhibitors available on the U.S. market currently. Like the factor Xa inhibitors, they may be taken orally and do not require laboratory monitoring. Dabigatran also has been demonstrated in meta-analyses to lead to fewer bleeding complications compared to warfarin. One potential advantage to dabigatran over the factor Xa inhibitors is that a reversal agent (idarucizumab) was recently approved by the FDA, which may be useful in the case of serious bleeding. Neither direct thrombin inhibitors or factor Xa inhibitors may be used in pregnant patients (unlike heparin, they cross the blood-placenta barrier) or in patients with significant renal disease.

Recommended Thromboprophylaxis Duration

The duration of anticoagulation depends on whether the patient has a first episode of DVT, ongoing risk factors for venous thromboembolic disease, and known thrombophilia.

Recommended duration of anticoagulation for a first proximal DVT or PE (American College of Chest Physicians 2016 guidelines):

First proximal DVT or PE	Recommended duration of anticoagulation	Evidence	
Provoked	From surgery or by a nonsurgical transient risk factor	Three months	1B
By a nonsurgical risk factor and low or moderate bleeding risk	1B		
Unprovoked	If bleeding risk is low or moderate	Three months. (May consider adding three more months after initial period)	1B
If bleeding risk is high	Three months	1B	
Associated with active cancer	High or low bleeding risk	Extended treatment (i.e. no scheduled stop date)	1 or 2B

When we describe LMWH dosing as fixed, what we mean is that dosing, although initially adjusted for weight, requires no further adjustment based on laboratory monitoring. Extended means six months or more.

Treatment of Thrombotic Disease with Inherited Thrombophilia

Some patients with inherited coagulation disorders are anticoagulated indefinitely after an episode of thrombotic disease.

Criteria for Recommended Screening for Inherited Thrombophilia

Although there are no absolute indications for screening for inherited thrombophilias, expert opinion on which patients are likely to benefit from such investigations includes patients with one of the following:

- Initial thrombosis occurring prior to age 40 without an immediately identified risk factor (e.g., idiopathic or unprovoked venous thrombosis).
- A family history of venous thromboembolism in a first-degree relative prior to the age of 50.

- Recurrent venous thrombosis.
- Thrombosis occurring in unusual vascular beds such as portal, hepatic, mesenteric, or cerebral veins.

If testing is being performed, it should not be done at time of VTE or while on anticoagulant therapy. There is currently no evidence to support any change in outcome when using such a strategy.

Studies

Predictive Value of Diagnostic Tests to Evaluate DVT vs Cellulitis

Venous Doppler of the lower extremity should tell you with good sensitivity and specificity if DVT is present.

Complete blood count	Elevated white blood cell count might make you consider cellulitis. However, a normal white count would not rule it out, nor is a leukocytosis specific enough to give you the diagnosis.
Culture and sensitivity	Would not tell you whether cellulitis is present, and is usually not useful in evaluating chronic ulcers.
D-dimer	Is a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is a relatively sensitive, but poorly specific test for the presence of DVT. While a negative result (low D-dimer concentration in the blood) practically rules out thrombosis, a positive result can indicate thrombosis, but does not rule out other potential causes, such as infection. Its main use, therefore, is to exclude thromboembolic disease where the probability is low.
MRI	Could identify the presence of thrombus. Expensive compared to venous doppler.

Clinical Reasoning

Differential of Unilateral Lower Extremity Edema

Most Likely Diagnoses

Lymphedema	• Lymphedema is generally painless, but patients may experience a chronic dull, heavy sensation in the leg. In the early stages of lymphedema, the edema is soft and pits easily with pressure. In the chronic stages, the limb has a woody texture and the tissues become indurated and fibrotic. • Lymphedema initially involves the foot and gradually progresses up the leg so that the entire limb becomes edematous.
Cellulitis	• Cellulitis is an acute inflammatory condition of the skin characterized by localized pain, erythema, swelling, and heat. • Small breaks of skin are associated with streptococcal infection, whereas staphylococcal cellulitis is commonly associated with larger wounds, ulcers, or abscesses. • Patients with diabetes are more susceptible to infections like cellulitis. Diabetic neuropathy causes an unawareness of abnormal pressure distribution. Ill-fitting shoes, cuts, or punctures can then lead to the development of ulcers. • Vascular disease with diminished blood supply contributes to the development of the lesion, and infection is common.
DVT	• Classic symptoms of DVT include swelling, pain, and discoloration in the affected extremity. • Physical examination may reveal the palpable cord of a thrombosed vein, unilateral edema, warmth, and superficial venous dilation. • Classic signs of DVT include Homan's sign (pain on passive dorsiflexion of the foot), edema, tenderness, and warmth. While difficult to ignore, they are of low predictive value and can occur in other conditions such as musculoskeletal injury, cellulitis, and venous insufficiency. • Chronic venous insufficiency may result from DVT and/or valvular incompetence. Following DVT, the valve leaflets become thickened and contracted so that they are incapable of preventing retrograde flow of blood; the vein becomes rigid and thick-walled. Although most veins recanalize after an episode of thrombosis, some may remain occluded. Secondary incompetence develops in distal valves because high pressures distend the vein and separate the leaflets. • Primary deep venous thrombosis can also occur without previous thrombosis. Patients with venous

	thrombosis often complain of a dull ache in the leg that worsens with prolonged standing and resolves with leg elevation. Examination reveals increased leg circumference, edema, and superficial varicose veins. • The presence of a thrombus in a vein may be accompanied by an inflammatory response in the vessel which may be minimal or may be characterized by granulocyte infiltration, loss of endothelium, and edema. This inflammatory process may also result in a low grade fever. • Smoking and obesity are the most robust risk factors in the development of DVT. Diabetes, sedentary lifestyle, hypertension, hyperlipidemia, increasing age, prolonged immobility, surgery, trauma, malignancy, pregnancy, estrogenic medications (e.g., oral contraceptive pills, hormone therapy, tamoxifen (Nolvadex)), congestive heart failure, hyperhomocystinemia, diseases that alter blood viscosity (e.g., polycythemia, sickle cell disease, multiple myeloma), and inherited thrombophilias are other potential risk factors in the development of DVT.
Venous insufficiency	• The edema of venous insufficiency can be differentiated from chronic lymphedema as venous insufficiency edema is softer, and there is often erythema, dermatitis, and hyperpigmentation along the distal aspect of the leg. Skin ulceration may occur near the medial and lateral malleoli. • Obesity is commonly associated with venous insufficiency.
Peripheral artery disease	• Peripheral artery disease (PAD) is the presence of systemic atherosclerosis in arteries distal to the arch of the aorta. As a result of the atherosclerotic process, patients with PAD develop narrowing of these arteries. • Patients with PAD have a history of claudication, which manifests as cramp-like muscle pain occurring with exercise and subsiding rapidly with rest. In addition, later in the course of the disease, patients may present with night pain, nonhealing ulcers, and skin color changes. • An ankle-brachial index (ABI) can be done to determine the presence of PVD. An ABI of < 0.9 is consistent with the disease. • Classic risk factors for PAD are smoking, diabetes mellitus, hypertension, and hyperlipidemia. Obesity (body mass index (BMI) > 30) increases risk for PAD as well. • Recent trials have added chronic renal insufficiency, elevated C-reactive protein levels, and hyperhomocysteinemia to the list of risk factors. • The greatest modifiable risk factor for the development and progression of PAD is cigarette smoking. Cigarette smoking increases the odds for PAD by 1.4 for every ten cigarettes smoked per day. • Arterial insufficiency is four times more prevalent in patients with diabetes than in those without diabetes. Nearly half of patients who've had diabetes for 20 years or more have PAD, usually below the knees.

Wells criteria for the diagnosis of DVT

Active cancer (treatment ongoing or within previous six months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the legs	1
Recently bedridden for more than three days or major surgery within four weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or more likely than that of deep vein thrombosis	-2

Low probability 0 or less, moderate probability 1–2, high probability 3 or more.

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