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Respiratory Medicine

DEATH STARTS IN YOUR LEGS: A COMPREHENSIVE REVIEW

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ABSTRACT The phrase "Death starts in your legs" metaphorically underscores the critical importance of peripheral health in overall well-being. A common cause of edema in the lower legs is chronic venous disease, a condition in which the veins in the legs cannot pump enough blood back up to the heart because the valves in the veins are damaged.Leg swelling, or edema, often serves as a visible indicator of underlying conditions, including Peripheral artery disease (PAD), Venous Thromboembolism (VTE), Pulmonary Thromboembolism (PTE), hypoalbuminemia, and endocrine disorders. Oedema is usually caused by standing or sitting in the same position for too long, eating excessive salty food, pregnancy, over overweight, blood pressure medicines, problems with the kidneys, heart, lungs, blood clotting, lymphatic filariasis, and an infection. One major circulatory condition that causes leg pain is Peripheral Artery Disease (PAD), which happens when arteries in the legs become narrowed or blocked due to a buildup of plaque (atherosclerosis) and plaque rupture, leading to suspicion of MI in various phases.

KEYWORDS : Restless legs syndrome (RLS), Ankle brachial index (ABI, Peripheral artery disease (PAD), Venous Thromboembolism (VTE) , Pulmonary Thromboembolism (PTE), Hypoalbuminemia

INTRODUCTION

Foot disorders, which impair the patient's ability to adequately utilize the calf muscle pump during ambulation, are another condition that contributes to edema.(1)

Leg edema, defined as a palpable swelling due to an increase in interstitial fluid volume, can manifest as visible swelling when fluid buildup in tissues reaches significant levels (2)

Unilateral or bilateral swelling, can be a benign inconvenience of severe underlying health issues affecting the cardiac, vascular, respiratory, renal, hepatic systems (3).

Restless legs syndrome (RLS), or Willis-Ekbom disease, is a common, chronic, multifactorial movement disorder of the limbs in which patients have an irresistible urge to move their legs (4)

Lower extremity peripheral artery disease (PAD) affects 8 million men and women in the United States (U.S.) (5)

Patients with PAD have a high prevalence of co-existing coronary artery and cerebrovascular atherosclerosis (6,7)

Increased risk of cardiovascular morbidity and mortality, compared to people without PAD (8,9).

Risk factors for PAD include smoking, diabetes, hyperlipidaemia, and hypertension (10).

PAD can be readily diagnosed in medical practice with the ankle brachial index (ABI), a ratio of Doppler-recorded systolic pressures in the lower and upper extremities (11).

People without PAD have ABI values ranging from 1.00 to 1.30. An ABI < 0.90 is approximately 70% sensitive and 95% specific for PAD (12).

Patients with PAD experience calf muscle ischemia during walking activity, when metabolic demands exceed oxygen supply, and calf muscle reperfusion during rest, when blood supply increases sufficiently to meet calf muscle oxygen requirements. (13,14).

Leg and ankle swelling can also be caused by blood clots and other serious medical conditions.15)

Leg edema, defined as a palpable swelling due to an increase in interstitial fluid volume, can manifest as visible swelling when fluid buildup in tissues reaches significant levels (16)

Either unilateral or bilateral swelling, can be a benign inconvenience affecting the cardiac, vascular, respiratory, renal, hepatic, or hematologic systems (17)

Accurate assessment, history-taking, and physical examination are essential for diagnosis and management (18)

Venous edema, defined as a swelling caused by an increase in protein-poor interstitial fluid, which is a consequence of increased (19,20)

Peripheral Artery Disease

PAD usually involves atherosclerotic disease in the abdominal aorta, iliac, and femoral arteries. Atherosclerotic plaque builds up slowly on the inside of arteries. In the early stages of PAD, the arteries compensate for the plaque buildup by dilating to preserve flow through the vessel. Eventually, the artery cannot dilate any further, and the atherosclerotic plaque starts to narrow the arterial flow lumen.In some cases, the cause of sudden ischemia may be emboli, either of cardiac origin or from atherosclerotic disease of the aorta. Emboli tend to be most common at sites of arterial bifurcation or where vessel branches have an abrupt take-off. The femoral artery is the most common site for emboli, followed by the iliac arteries, the aorta, and the popliteal arteries. The hemodynamic consequences of atherosclerosis depend

on the degree of arterial narrowing. The muscles of the lower extremity require increased blood flow during ambulation to meet the increased energy demand. Patients with PAD reach a point during walking at which collateral blood flow is maximized and cannot provide any more perfusion to the lower extremity muscles. Lowering the energy demands of the muscle allows the blood supply to "catch up," and the ischemic symptoms resolve. (22)

Patients with PAD usually have enough collateral blood flow that they only have symptoms during activities that increase energy demand, such as walking. (23)

Patients with PAD have a high prevalence of co-existing coronary artery and cerebrovascular atherosclerosis (24,25) and an increased risk of cardiovascular morbidity and mortality, compared to people without PAD (26).

Risk factors for PAD include smoking, diabetes, hyperlipidaemia, and hypertension (27).

PAD can be readily diagnosed in medical practice with the ankle brachial index (ABI), a ratio of Doppler-recorded systolic pressures in the lower and upper extremities (28).

People without PAD have ABI values ranging from 1.00 to 1.30. An ABI < 0.90 is approximately 70% sensitive and 95% specific for PAD (29).

Additional risk factors for PAD include diabetes, hyperlipidemia, hypertension, race, and ethnicity (30)

Venous Thromboembolism (VTE)

It is categorised as deep venous thrombosis (DVT) and pulmonary embolism (PE). To diagnose VTE, non-invasive, cost-effective diagnostic algorithms, including clinical probability assessment and D-dimer measurement, may be employed, followed by compression ultrasonography for suspected DVT patients and multidetector computed tomography angiography for suspected PE patients. There are pharmacological and mechanical interventions to manage and prevent VTE. Excess bleeding is one of the major risk factors for pharmacological interventions. (31)

Deep Venous Thrombosis (DVT)

Most patients present with symptoms when distal DVT extends to the popliteal and femoral veins and other proximal veins.DVT can lead to complications such as postphlebitic syndrome, PE, and death (32).

DVT reoccurs in about 10% of patients who may develop severe postthrombotic syndrome within 5 years (33,34)

DVT usually initiates in the calf area of the leg. The majority of thrombi form in the deep veins below the popliteal trifurcation (distal DVT) most likely to resolve spontaneously with no symptoms. (35)

Pulmonary Embolism (PE)

PE symptoms, such as new or worsening dyspnoea, chest pain, or sustained hypotension with no alternative cause, occur in about 30–40% of patients with VTE (36)

The survival rate for patients with PE is worse than DVT, as sudden death is the initial clinical presentation of 25% of these patients (37).

Hypoalbuminemia and Bilateral Edema

Hypoalbuminemia is characterized by low levels of serum albumin, it is a significant contributor to bilateral leg edema. Albumin maintains oncotic pressure, which is essential for keeping fluid within the vascular compartment. In conditions like nephrotic syndrome, liver disease, and malnutrition, decreased albumin levels lead to reduced plasma oncotic pressure. This reduction allows fluid to leak into the interstitial spaces, causing edema.

Nephrotic Syndrome and Swollen Feet?

Nephrotic syndrome is a kidney disorder characterized by excessive protein loss in the urine, leading to hypoalbuminemia. The primary causes of nephrotic syndrome include focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease. The loss of albumin reduces the osmotic pressure within blood vessels, causing fluid to accumulate in tissues, resulting in edema. This condition often manifests as swelling around the eyes, legs, and abdomen, and can lead to complications such as infections and blood clots. (38)

Liver Disease

The Cracks in Your Feet Might be Telling You Something About Your Liver.

The liver plays a crucial role in synthesizing albumin. Conditions such as cirrhosis and chronic hepatitis can impair albumin production, leading to hypoalbuminemia. The reduced albumin levels diminish the blood's ability to retain fluid, causing fluid to leak into surrounding tissues and resulting in edema. In advanced liver disease, this can lead to ascites, pleural effusion, and peripheral edema. One way in which hepatic disease can cause bilateral edema is through the impairment of the liver's ability to synthesize albumin. This, in turn, will decrease the oncotic capillary pressure, ultimately allowing more fluid to leave the blood vessels and enter the extracellular space. Liver failure is also a contributing factor to peripheral edema due to increased hydrostatic pressure in systemic capillaries resulting from portal vein congestion. (39)

What Deficiencies Cause Weakness of the Legs

Several vitamin and mineral deficiencies can contribute to leg weakness, including Vitamin D,E, B12, folate, iron, and Potassium. Potassium deficiency (Hypokalaemia) can cause muscle weakness, including in the legs, along the symptoms like fatigue, due to reduced oxygen supply to muscles. Vitamin B12 and folate deficiencies can cause nerve damage and muscle weakness, and pain, including inthe legs.

Iron deficiency may be one of the reasons for RLS-restless leg syndrome. Restless legs syndrome (RLS), or Willis-Ekbom disease, is a common, chronic, multifactorial movement disorder of the limbs in which patients have an irresistible urge to move their legs (40)

Malnutrition, particularly protein-energy malnutrition, can lead to hypoalbuminemia. Insufficient dietary intake of protein reduces albumin synthesis, leading to decreased oncotic pressure and subsequent edema. Kwashiorkor, a severe form of malnutrition, is characterized by hypoalbuminemia and generalized edema, including swelling of the legs.

Hypothyroidism and Graves' Disease (Thyroid Eye Disease)

Endocrine disorders, particularly hypothyroidism and Graves' disease, can manifest as leg swelling.

Hypothyroidism and Myxedema

Hypothyroidism leads to myxedema, where mucopolysaccharides accumulate in tissues, causing non-pitting edema. This accumulation is due to the deposition of glycosaminoglycans in the dermis, leading to thickened skin and swelling. Myxedema can affect various body parts, including the legs, leading to characteristic swelling.

Graves' Disease and Pretibial Edema

Graves' disease, an autoimmune disorder causing hyperthyroidism, can also present with leg swelling. (41)

A rare but notable manifestation is pretibial myxedema, characterized by thickened, waxy skin over the shins. This condition is associated with the deposition of hyaluronic acid in the skin and is often seen in patients with severe thyroid disease.

Non-steroidal Anti-Inflammatory Drugs NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agents (42)

These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and are used as opioid-sparing agents in certain acute trauma cases (43,44)

NSAIDs commonly cause water retention, which can lead to swelling in the legs and ankles. This tends to be more likely in older adults and people with kidney problems. Typically, the swelling will go away once you stop taking the medication. But NSAIDs can also make heart failure worse. NSAIDs can cause drug-induced edema (swelling) by disrupting normal kidney function and leading to fluid retention. This can manifest as peripheral edema, especially in the legs and ankles. NSAIDs can also contribute to angioedema, a type of edema affecting deeper tissues, sometimes causing swelling of the face, lips, or tongue.

Renal Dysfunction:
NSAIDs can impair kidney function, leading to reduced water and sodium excretion. This can result in fluid retention and swelling.

Mechanism:
NSAIDs inhibit the production of prostaglandins, which play a role in regulating blood vessel dilation and fluid balance in the kidneys. By blocking these prostaglandins, NSAIDs can cause vasoconstriction and reduce blood flow to the kidneys, leading to impaired filtration and fluid retention. Increased Risk: Individuals with pre-existing conditions like heart failure, hypertension, or kidney disease are at a higher risk of developing NSAID-induced edema.

Types of Oedema:
NSAIDs can cause various types of edema, including: Peripheral edema: Swelling in the extremities, particularly the legs and ankles, due to fluid accumulation.

Angioedema:
Swelling of deeper tissues, including the face, lips, tongue, and throat, which can be life-threatening if it affects the airways

Corticosteroids --Oedema
Corticosteroids can induce edema as a side effect due to their influence on the body's water and salt balance. This is particularly noticeable with long-term or high-dose corticosteroid use.

Mechanism
Corticosteroids, especially those with mineralocorticoid activity, alter the body's ability to regulate sodium and water, leading to fluid retention. This can manifest as swelling in the lower extremities, face, or other areas.

Calcium Channel Blockers (CCBs)
Induce peripheral edema, a common side effect primarily due to increased capillary hydrostatic pressure caused by selective pre-capillary arteriolar dilation. This effect leads to fluid leakage into the interstitial space, resulting in swelling, particularly in the lower extremities.

Mechanism
Pre-capillary vasodilation: CCBs, particularly dihydropyridines like amlodipine and nifedipine, primarily dilate precapillary arterioles, increasing pressure in the capillaries. Increased capillary hydrostatic pressure: This pressure difference between the capillaries and the interstitial space drives fluid leakage out of the capillaries and into the surrounding tissues.

Individual Susceptibility
Factors like age, gender (women are more susceptible), and obesity can influence edema development. Upright posture: Edema is more pronounced when standing or sitting for extended periods, as gravity contributes to fluid pooling in the lower extremities.

Thiazolidinediones (TZDs)
A class of antidiabetic drugs can cause edema as a side effect, particularly when used in combination with insulin or in patients with heart failure. This fluid retention can manifest as peripheral edema, but in some cases, it can progress to more serious conditions like pulmonary edema and congestive heart failure.

Mechanism of Oedema
Renal Sodium Retention: TZDs, like pioglitazone and rosiglitazone, can affect sodium handling in the kidneys, leading to increased sodium reabsorption. Increased Vascular Permeability: TZDs can also increase the permeability of blood vessels, allowing fluid to leak into surrounding tissues.

Increased Plasma Volume
Fluid retention can lead to an increase in plasma volume, diluting red blood cells and reducing haematocrit. Possible Involvement of PPAR-gamma: TZDs activate peroxisome proliferator-activated receptor gamma (PPARγ), which may play a role in the sodium reabsorption and fluid retention processes.

Erysipelas
It is usually caused by the group A Streptococcus bacteria. The condition may affect both children and adults. Some conditions that can lead to erysipelas are: A cut in the skin. Erysipelas is primarily caused by the bacterium Streptococcus pyogenes, often referred to as Group A streptococci. It's a superficial bacterial skin infection that spreads to the lymphatics. While Group A streptococci are the most common culprit, other bacteria, like Staphylococcus aureus, can also cause erysipelas. The infection often enters through breaks in the skin, such as cuts, wounds, or insect bites. Here's a more detailed breakdown: Primary Cause: Group A streptococci (Streptococcus pyogenes). Entry Points: Breaks in the skin, like cuts, wounds, insect bites, or even surgical incisions.

Other Potential Causes
Staphylococcus aureus (including MRSA), Klebsiella pneumoniae, and other bacteria. Risk Factors: Skin conditions like eczema, impetigo, fungal infections, and wounds; injuries; a weakened immune system; and conditions like diabetes or venous insufficiency.

Unilateral Lower Extremity Swelling
Often, a key sign of deep vein thrombosis (DVT), can be mimicked by various other conditions that cause swelling or compression of the iliac veins. These include Baker's cyst rupture, cellulitis, musculoskeletal injuries, and extrinsic compression of the veins from tumors or other masses.

Cellulitis:
Inflammation and infection of the soft tissues, often in the leg, can cause swelling, redness, and pain, which can be mistaken for DVT. Musculoskeletal Injuries: Injuries to the muscles and tissues in the leg can lead to swelling and pain, potentially mimicking the symptoms of a DVT. Extrinsic Compression of Veins: Tumors, lymphadenopathy, or other masses can compress the veins, leading to swelling and pain in the leg.

Swollen Feet During Pregnancy:
Pregnancy is associated with several dermatological, vascular, neurological, and musculoskeletal changes. These include restless leg syndrome and ligament laxity, respectively (45)

Pregnant women also present with several functional and structural malformations, which include swelling, changes in posture, and pain and edema in the lower limbs (46)

Venous insufficiency occurs due to the changes that develop during pregnancy. The enlargement of the abdomen as the baby grows places increased pressure on the circulatory system, compromising the blood flow to the lower limbs. As a result, there is an insufficient nutrient and oxygen supply, causing cramps and pain. (47)

Varicosities have also been associated with pregnancy and occur due to elevated blood volume and decreased venous return. Edema presents as a result of an increased hydrostatic pressure caused by longstanding compression of the uterus and femoral vessels (48)

It has been established through various research studies that pregnancy alters the general health of women in many ways (49,50)

1. Venous Thromboembolism (VTE) and Pulmonary Thromboembolism (PTE)

1. Importance of Leg Examination in VTE Evaluation

- Deep vein thrombosis (DVT) is the major source of pulmonary thromboembolism.
- Most emboli originate from deep veins of the lower limbs (especially the calf veins, femoral, and iliac veins).
- Physical signs in the leg can provide early clues:
- Swelling (unilateral)
- Redness
- Warmth
- Pain or tenderness (especially calf tenderness)
- Dilated superficial veins
- Thus, careful examination of both legs is crucial in any suspected case of venous thromboembolism.

2. When to Suspect Venous Thromboembolism (VTE)

- Recent immobilization (e.g., surgery, fractures, long travel)
- Active cancer
- Pregnancy or postpartum period
- Use of oral contraceptives or hormone replacement therapy
- Previous DVT or PE history
- Obesity
- Smoking

- Symptoms to look for:
- Leg pain, swelling, or tenderness
- Skin discoloration

3. When to Suspect Pulmonary Thromboembolism (PTE)

- Sudden onset of:
- Shortness of breath (dyspnoea)
- Chest pain (especially pleuritic)
- Hemoptysis (coughing blood)
- Syncope (fainting)
- Tachypnea (rapid breathing)
- Tachycardia (rapid heart rate)
- Unexplained hypoxia (low oxygen saturation)
- Signs of DVT with respiratory symptoms raise a strong suspicion.

4. Scoring Systems

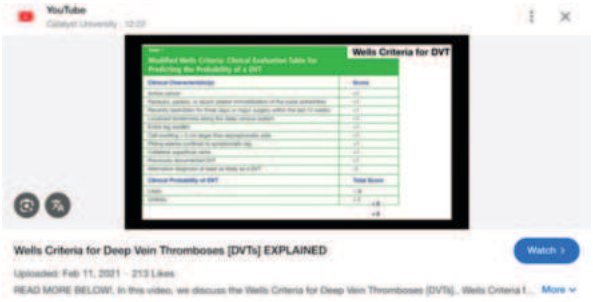
Scoring systems help to assess the clinical probability of VTE or PTE:

Common Scores:

- Wells Score for DVT
- Wells Score for PE
- Revised Geneva Score
- Pulmonary Embolism Severity Index (PESI)

Purpose:

- To decide if further testing is needed (like D-dimer, imaging).
- To stratify risk (low, intermediate, high probability).



Scoring and Interpretation

- **High probability**: ≥3 points
- **Moderate probability**: 1–2 points
- **Low probability**: 0 or less

(51)

Wells Score for PE

Clinical Feature	Points
Clinical signs and symptoms of DVT	+3
PE is the most likely diagnosis	+3
Heart rate >100 bpm	+1.5
Immobilization ≥3 days or surgery within past 4 weeks	+1.5
Previous objectively diagnosed PE or DVT	+1.5
Hemoptysis	+1
Malignancy (ongoing, treated in last 6 months, or palliative)	+1

Interpretation	Clinical Probability
>6	High probability
2 to 6	Moderate probability
<2	Low probability

Interpretation

Score	Clinical Probability
>6	High probability
2 to 6	Moderate probability
<2	Low probability

Alternatively, a **simplified 2-tier model**:

Score	Interpretation
>4	PE likely
≤4	PE unlikely

5. Blood Investigations for Pulmonary Thromboembolism

- D-dimer:
- Elevated in VTE but non-specific.
- Good negative predictor if low (rules out PE if clinical probability is low).
- Arterial blood gas (ABG):
- May show hypoxemia, hypocapnia, and respiratory alkalosis.
- Cardiac markers:
- Troponin: May be elevated if right heart strain.
- BNP (Brain Natriuretic Peptide): May rise with right ventricular dysfunction.
- Complete blood count (CBC):
- To look for anemia, leukocytosis.
- Coagulation profile:
- PT, aPTT, INR are important if considering thrombolysis.
- Blood group and thrombophilia screening (in young or recurrent VTE cases).

6. How to Confirm Pulmonary Thromboembolism

Diagnostic Tests:

- CT Pulmonary Angiography (CTPA):
- Gold standard imaging.
- Direct visualization of thrombus in pulmonary arteries.
- Ventilation-Perfusion (V/Q) scan:
- Used if CTPA contraindicated (e.g., renal failure, allergy to contrast).
- Compression Ultrasound of the legs:
- For DVT confirmation.
- Echocardiography:
- Signs of right ventricular strain.
- Useful if the patient is unstable and cannot be shifted for CTPA.

7. Complications of Pulmonary Thromboembolism

- Acute right heart failure (cor pulmonale)
- Pulmonary infarction (lung tissue death)
- Recurrent embolism
- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Sudden cardiac death
- Hypoxia and respiratory failure

8. How Pulmonary Embolism Leads to Right Heart Failure

- Embolus blocks blood flow in the pulmonary arteries.
- Increases pulmonary vascular resistance.
- The right ventricle has to pump against this high resistance.
- Right ventricular dilation and dysfunction occur.
- Reduced output from the right heart leads to:
- Systemic venous congestion (raised JVP, hepatomegaly, edema)
- Decreased blood flow to the lungs (hypoxia)
- Ultimately, if severe, it leads to cardiogenic shock and death.

Laboratory Tests for Edema Evaluation

Diagnosing the underlying cause of leg edema involves a combination of clinical assessment and laboratory tests:

- **Serum Albumin Levels:** Low levels indicate hypoalbuminemia, supporting diagnoses like nephrotic syndrome or liver disease.
- **Thyroid Function Tests:** Elevated TSH and low T3/T4 levels suggest hypothyroidism, while suppressed TSH with elevated T3/T4 levels indicate hyperthyroidism.
- **Urinalysis:** The Presence of proteinuria can point to nephrotic syndrome.
- **Liver Function Tests:** Abnormal results may indicate liver disease contributing to hypoalbuminemia.

CONCLUSION

Leg swelling is more than a mere cosmetic concern; it is a significant clinical sign of systemic health issues. Hypoalbuminemia, resulting from conditions like nephrotic syndrome, liver disease, and malnutrition, can lead to bilateral edema. Endocrine disorders such as hypothyroidism and Graves' disease further complicate this picture, with myxedema and pretibial myxedema, respectively, contributing to leg swelling. Early detection and appropriate management of these underlying conditions are crucial in preventing severe complications and improving patient outcomes. In conclusion, leg edema is a multifactorial condition with a wide range of underlying causes, primarily venous insufficiency, congestive heart failure, and nephrotic syndrome. The interplay between leg health and systemic conditions underscores the importance of holistic assessment.

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