

Evaluation and management of peripheral edema

Edema can be treated systematically and comprehensively, based on an understanding of the pathophysiologic mechanisms involved. This approach encourages accurate diagnosis while ensuring safety and cost-effectiveness.

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Edema is a palpable swelling produced by expansion of the interstitial fluid volume and is often nonspecific. When massive and generalized, the excess fluid accumulation is called anasarca. A variety of clinical conditions, ranging from the benign to the potentially life threatening, is associated with the development of peripheral edema. These include common conditions such as heart failure (HF), cirrhosis, and nephrotic syndrome (NS), but edema may also be idiopathic (see Table 1, page 31).¹ A systematic approach to the patient with edema allows for prompt and cost-effective diagnosis and treatment.¹

Anatomy and pathophysiology

Total body water is divided between the intracellular and extracellular spaces. The extracellular space, which comprises about one third of total body water, is composed of the intravascular plasma volume (25%) and the extravascular interstitial spaces (75%).² According to Starling's law, the physiologic forces involved in maintaining the balance of water between these two compartments include the gradient between extravascular and intravascular hydrostatic pressures, differences in oncotic pressures within the interstitial space and plasma, and the permeability of the blood vessel wall.³ Fluid and filtered proteins from the interstitial space are collected by the lymphatic system and returned to the

vascular compartment. Peripheral edema results from a disturbance in this delicate equilibrium with net filtration out of the vascular space or from impaired return of fluid by lymphatics in the interstitial space.^{4,5}

Alteration of Starling forces plays a central role in the pathophysiology of edema. Increased venous pressure due to central or regional venous obstruction or to an expansion in plasma volume is transmitted to the capillary bed, thereby increasing hydrostatic pressure and predisposing to edema. Conversely, local autoregulation

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Learning objectives

- Discuss the pathophysiologic mechanisms that contribute to peripheral edema
- Describe the components of a cost-effective work-up, including the history, physical examination, and diagnostic tests
- Review nonpharmacologic therapy for peripheral edema, with an emphasis on diet and lifestyle modification
- Review pharmacologic therapies, with particular attention to the use of diuretics

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IN THIS ARTICLE

Key Points

- Peripheral edema may be a nonspecific finding common to many diseases, ranging from the benign to the potentially life threatening.
- A comprehensive history and physical examination with basic laboratory tests can yield an accurate diagnosis in the majority of cases.
- The treatment of edema consists of reversing the underlying disorder.
- Dietary sodium and fluid restriction constitute the mainstay of nonpharmacologic treatment, with diuretic therapy added as needed.

Competencies

Medical knowledge	◆◆◆◆◆
Interpersonal & communication skills	◆◆
Patient care	◆◆
Professionalism	◆
Practice-based learning and improvement	◆
Systems-based practice	◆

For an explanation of competencies ratings, see the table of contents.

by smooth muscle sphincters on the precapillary (or arterial) side protect the capillary bed from increases in systemic arterial pressure, which explains why hypertensive patients do not have edema despite elevated BP.^{6,7}

An increase in capillary permeability due to vascular injury is a key event in edema formation resulting from local inflammation. Capillary permeability is under the control of cytokines, circulating vasodilatory prostaglandins, and nitric oxide.⁸ Increase in capillary permeability promotes the development of edema both directly and indirectly by permitting albumin to move into the interstitium, thereby diminishing the oncotic pressure gradient.

The lymphatics play an essential role in reabsorption of interstitial fluid and proteins, returning them to the central circulation. Lymphatic obstruction is an unusual cause of edema (called lymphedema) that is most often seen with nodal enlargement due to malignancy and with surgical removal of lymph nodes, such as during radical mastectomy. In certain disease conditions such as myxedema, the lymphatic system is overwhelmed because of the marked increase in interstitial accumulation of albumin and other proteins.⁹

Multiple renal and neurohumoral factors control fluid and electrolyte homeostasis. In certain disease states, such as chronic HF and cirrhosis, the neurohumoral cas-

cade that attempts to maintain effective circulating volume becomes maladaptive, leading to a cycle of further sodium and water retention. In chronic edematous states, end-organ resistance to natriuretic peptides inevitably occurs, which explains the sodium retention in these conditions despite high circulating levels of these peptides.^{10,11}

History and physical examination

Use a multisystem approach when evaluating a patient with edema. Of particular importance is excluding major organ system dysfunction, especially cardiac, liver, and renal dysfunction. Document the location of the edema, its progression, and whether it occurs intermittently or persistently. Analyze these clinical findings in relation to the patient's medical history of coronary artery disease, renal disease, liver disease, and so forth. Ask questions such as the following:

- Do the rings on your fingers get tight?
- Have you had to let your belt out?
- Have your clothes or shoes gotten too tight?¹²

Pay special attention to the patient's medications; several can cause edema, such as NSAIDs, calcium channel blockers, and estrogens.¹³⁻¹⁶ Assess whether patients who are already taking a diuretic to treat peripheral edema are adhering to their drug regimen.

Also, obtain a thorough dietary history, paying careful attention to the patient's dietary sodium intake, total daily fluid intake, and adherence to special dietary restrictions (see www.heartfailure.org and www.kidney.org for special dietary instructions for salt and fluid restriction).

The physical examination In addition to the standard physical examination, chart the patient's weight and note general appearance, paying special attention to the edema with respect to location, symmetry, pitting or nonpitting appearance, tenderness, and associated skin changes, such as ulceration and rubor. Look for ascites. Evaluating the peripheral and central venous systems may shed light on the pathogenesis of edema. Lastly, assess the severity of edema with a method such as the four-point scale (+1, slight, to +4, very marked), the presence of sacral edema, and the height in the case of lower extremity edema.¹²

Diagnostic testing Order simple, safe, and cost-effective tests, including a chemistry panel and urinalysis to evaluate renal and liver function and albumin levels to assess nutritional status. Consider measuring the thyrotropin level to rule out hypothyroidism. In cases where screening for a cardiac etiology is required, an ECG and chest radiograph may be helpful in assessing cardiac function. When considering diagnostic tests in the context of a potentially long list of etiologies, a comprehensive history and physical examination, along

with basic metabolic laboratory tests, can yield an accurate diagnosis in the majority of cases; expensive testing is usually unnecessary.

Differential diagnosis

Many safety factors must be overcome before edema develops. Because the interstitial tissues easily accommodate several liters of fluid, a patient's weight may increase nearly 10% before pitting edema is evident.¹ Also, the gradient favoring filtration must increase by at least 15 mm Hg before edema can be detected.¹⁷

Three factors contribute to this protective response. The first is increased lymphatic flow that initially removes the excess filtrate. For example, with pulmonary edema due to HF, the rate of increase in lung liquid accumulation at any given elevation in pulmonary capillary pressure is related to the functional capacity of the lymphatics. Lymphatic functional capacity is influenced by individual factors and the acuteness of the hemodynamic change. With acute rises in pulmonary capillary pressures, the pulmonary lymphatic system does not have an increased capacity to remove fluid; thus, pulmonary edema occurs at pulmonary artery capillary pressures as low as 18 mm Hg. In contrast, patients with chronic HF have an increased lymphatic capacity and do not develop pulmonary edema until much higher pulmonary capillary pressures (greater than 25 mm Hg) are reached.¹⁸

The second form of protection is fluid entry into the interstitium that eventually raises the interstitial hydraulic pressure.¹⁷ Fluid entry into the interstitium that also lowers the interstitial oncotic pressure, both by dilution and by lymphatic-mediated removal of interstitial proteins, comprises the third protective factor.¹⁹

Heart failure Systolic and diastolic dysfunction elevates venous pressure, which in turn increases capillary hydrostatic pressure. Additionally, the low output state activates neurohormonal mechanisms that initially are aimed at restoring adequate arterial perfusion. Eventually, the resulting extravasation of fluid outpaces the ability of the lymphatic system to return fluid to the vascular space, resulting in pitting edema. Right-sided ventricular dysfunction leads to peripheral edema, whereas left-sided ventricular failure (LVF) produces pulmonary edema.⁷ Although the capacity of the lymphatic system to remove fluid is increased with HF, the lymphatic system will be overwhelmed in acute cases

Constrictive pericarditis/restrictive cardiomyopathy

Clinically, these conditions are sometimes indistinguishable from right heart failure (RHF). All these diagnoses may manifest with peripheral edema, elevated jugular venous pressure, hepatic congestion, and ascites. Also, because of its insidious onset, ascites and cardiac cirrhosis resulting in liver dysfunction may ensue and patients may receive a misdiagnosis of primary hepatic cir-

rhosis.^{1,20} Conclusive diagnosis may require transthoracic echocardiography, right heart catheterization, and tissue biopsy.¹

Nephrotic syndrome NS comprises a group of disorders characterized by severe proteinuria, hypoalbuminemia, hyperlipidemia, and edema. The exact mecha-

TABLE 1
Causes of peripheral edema

Cardiac
Constrictive pericarditis
Left ventricular systolic and diastolic dysfunction
Restrictive cardiomyopathy
Right ventricular systolic dysfunction
Tricuspid valvular disease
Pulmonary
Chronic obstructive pulmonary disease
Obstructive sleep apnea
Pulmonary hypertension
Renal
Acute/chronic renal failure
Nephrotic syndrome
Venous
Deep venous thrombosis
Inferior venacaval/iliac compression
Venous insufficiency
Other
Allergic reactions (angioedema)
Burns
Idiopathic causes
Increased capillary permeability
Liver failure
Lymphedema
Malnutrition/vitamin deficiencies/malabsorption syndromes
Medications
Myxedema
Pregnancy/preeclampsia
Proteinuria/hypoalbuminemia

TABLE 2

Pharmacokinetics of diuretic drugs

Diuretic	Oral bioavailability (%)	Elimination half-life (h)			
		Normal subjects	Patients with renal insufficiency	Patients with cirrhosis	Patients with heart failure
LOOP					
Furosemide	10-100	1.5-2	2.8	2.5	2.7
Bumetanide	80-100	1	1.6	2.3	1.3
Torsemide	80-100	3-4	4-5	8	6
THIAZIDE					
Bendroflumethiazide	ND	2-5	ND	ND	ND
Chlorthalidone	64	24-55	ND	ND	ND
Chlorothiazide	30-50	1.5	ND	ND	ND
Hydrochlorothiazide	65-75	2.5	Increased	ND	ND
Hydroflumethiazide	73	6-25	ND	ND	6-28
Indapamide	93	15-25	ND	ND	ND
Polythiazide	ND	26	ND	ND	ND
Trichlormethiazide	ND	1-4	5-10	ND	ND
DISTAL					
Amiloride	Conflicting data	17-26	100	Negligible change	ND
Triamterene*	>80	2-5	Prolonged	No change	ND
Spironolactone	Conflicting data	1.5	No change	No change	ND
Spironolactone, active metabolites	—	>15	ND	ND	ND

Key: ND, not determined.

*Values are for the active metabolite.

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nism for edema formation is uncertain, although one possibility includes reduced colloid oncotic pressure due to massive kidney protein loss. Loss of circulating volume also triggers neurohormonal mechanisms that perpetuate the edema formation cycle.

The above mechanisms do not appear to explain edema formation in most adult patients; however, salt retention seems to have a substantial effect.²¹ The reduction in interstitial oncotic pressure has important implications for the role of hypoalbuminemia in edema formation and for the tendency of edema to form at different sites, but whether this plays a primary role in NS is debatable. In the absence of severe hypoalbuminemia,

edema in NS and renal disease is primarily due to increased renal sodium retention.^{22,23}

Hypoproteinemia Conditions such as acute nutritional deficiency, protein-losing enteropathies, and severe liver disease can lead to hypoproteinemia. Albumin is important for maintaining plasma oncotic pressure; a level below 2 g/dL of plasma often results in generalized edema.¹

Cirrhosis Severe hypoalbuminemia with plasma albumin levels less than 2 g/dL can occur when severe liver disease ensues. However, the most important mechanism behind edema formation in cirrhosis may be decreased effective circulating volume secondary to

splanchnic vasodilation. This results in a neurohumoral cascade of events leading to sodium and water retention by the kidneys. In this regard, the mechanism of edema in cirrhosis resembles that in HF and NS.²⁴

Drug-induced edema Certain medications can induce edema by enhancing sodium and water reabsorption by the kidneys. Potent vasodilators such as minoxidil and diazoxide are good examples. Other drugs that can cause edema include calcium channel blockers, which lead to capillary leakage due to dilation of the precapillary sphincter,¹³ and the NSAIDs, which induce edema formation through different mechanisms by inhibiting renal prostaglandin synthesis. They can also exacerbate edema in patients with underlying HF or cirrhosis.¹⁴ Antidepressants, estrogens, corticosteroids, and COX-2 inhibitors can also cause peripheral edema.

Pregnancy The physiologic mechanisms underlying edema in pregnancy include increased plasma volume and sodium retention, possibly secondary to increased antinatriuretic hormones such as aldosterone and desoxycorticosterone. Other causes include decreased plasma protein concentration and increased capillary hydrostatic pressure late in pregnancy from mechanical compression of the inferior vena cava and iliac veins.^{25,26}

Lymphedema This nonpitting, less common form of edema usually involves a limb and is caused by impaired lymphatic transport, which leads to pathologic accumulation of protein-rich lymphatic fluid in the interstitium. Lymphedema is classified as primary or secondary. Primary lymphedema includes congenital hereditary lymphedema, Meige's disease, and other rare congenital disorders.^{27,28} Secondary lymphedema, far more common, is caused by lymph node dissection, radiation, malignant obstruction, and infection. In developed countries, lymph node dissection and radiation are the most common causes of lymphedema.²⁷ In developing countries, lymphatic obstruction from parasitic infection is the most common cause, with filariasis being the most widespread infection worldwide.²⁷

Myxedema Both hypothyroidism and hyperthyroidism can precipitate peripheral edema, but hypothyroidism is a more common cause. Localized edema frequently occurs on the eyelids, face, and dorsum of the hand in these conditions. The mechanism of myxedema is not fully understood. Increased capillary permeability results in the accumulation of proteins and mucopolysaccharides in the interstitium, followed by water and sodium movement. Concomitant expansion in total body water and increased total body sodium then occurs.²⁹⁻³¹

Idiopathic edema A poorly understood syndrome of abnormal fluid retention that primarily affects premenopausal women, idiopathic edema includes entities such as cyclical edema, periodic edema, fluid retention syndrome, and orthostatic edema. Key features are peri-

odic episodes of edema in women who have weight changes not clearly related to the menstrual cycle.³² The diagnosis is usually one of exclusion. It is most common in the third and fourth decades and is usually associated with psychological and emotional disturbances and concomitant misuse/abuse of diuretics or laxatives.^{33,34}

Lipedema is commonly mistaken for peripheral edema or lymphedema, but it occurs almost exclusively in young women and characteristically spares the feet. Onset, which is usually insidious, is often apparent shortly after puberty.³⁵

Treatment and follow-up

The treatment of edema consists of reversing the underlying disorder, if possible; hence, an accurate diagnosis is crucial. Dietary sodium and fluid restriction constitute the mainstay of nonpharmacologic treatment. Before using diuretics, the clinician must recognize the hemodynamic consequences of fluid removal. In cases such as pulmonary edema, where edema is life threatening, pursue immediate treatment and rapid fluid removal. Removing excess fluid can proceed more slowly in patients who have less dangerous edematous states.

Use caution to avoid major fluid shifts, hemodynamic instability, and electrolyte disturbances. For example, in patients with NS who undergo excessive and rapid fluid removal through diuretic therapy, concomitant intravascular volume depletion can lead to further kidney damage. In patients with cirrhosis, overzealous fluid removal can cause life-threatening hypokalemia, metabolic alkalosis, and rapid fluid shifts induced by diuretics, as well as hepatic coma or the hepatorenal syndrome. Use a cautious combination of patient education, diet modification, and diuretics when appropriate.¹ Consider specialty referral or consultation to deal with underlying causes.

Diuretic therapy Constituting the mainstay of pharmacologic therapy, diuretics include loop, potassium-sparing, and thiazide agents (see Table 2, page 32). Loop

Online resources

National Library of Medicine
www.nlm.nih.gov/medlineplus

National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov

National Kidney Foundation
www.kidney.org

American Liver Foundation
www.liverfoundation.org

Heart Failure Online
www.heartfailure.org

diuretics, which are usually the most effective, have short plasma half-lives. For example, furosemide has a half-life of 1.5 to 2 hours,³⁶ so several doses per day are required to maintain natriuresis. Since response to each loop diuretic is patient specific, a threshold level of the drug at the site of action must be attained for maximal response. Exceeding this level will not increase diuresis. Because the mechanisms of action are the same, changing to a second loop diuretic will not work if an adequate dosage of the first is not effective.³⁶

Consider adjusting the dosage for renal insufficiency, since larger dosages may be necessary to attain the threshold amount of drug in the tubular fluid.³⁶ The efficacy of diuretics becomes minimal when the glomerular filtration rate is less than 20 mL/min and may be null when it is less than 10 mL/min. Different classes of diuretics work on different nephron sites, so diuretic combinations from different classes may be used. Reducing sodium reabsorption in the distal nephron by adding a thiazide or potassium-sparing diuretic may improve diuresis when loop diuretics alone do not work.

Prevention and patient education Take the time to educate patients about the side effects of their medication. Instruct them to avoid OTC medications since some, including NSAIDs, may cause drug-induced edema.¹⁴ When considering patient education, emphasize also that not all patients with edema are alike. A number of Internet sites have information about edema that may be useful (see "Online resources," page 33).

Sodium and fluid restriction Consider referring to a registered dietitian those patients with chronic conditions leading to peripheral edema. A dietitian can assess a patient's nutritional status, design an individualized diet, and work with a clinician as a part of a comprehensive team approach. Salt restriction is the mainstay of dietary management; the sodium recommended daily allowance (RDA) is 2,400 mg/d, but clinicians usually recommend 2,000 mg/d for most patients with peripheral edema. Remind patients that sodium intake includes table salt as well as salt already present in foods. Instruct them to check food labels for high salt content and to use fresh ingredients in place of canned or processed foods with especially high sodium content. In addition to restricting salt, patients should restrict fluids to a total of 2 liters per day; the water content in foods alone is often enough to achieve this limit.

Lifestyle modification For most patients with peripheral edema, exercise and weight reduction can decrease symptoms and potentiate the effect of dietary and pharmacologic fluid removal. In those with venous stasis, compression stockings increase venous return to the heart and decrease lower extremity edema. Oxygen therapy and/or continuous positive airway pressure are important adjunctive therapies in patients with hypoxia

secondary to obstructive pulmonary disease and obstructive sleep apnea leading to pulmonary hypertension.³⁷

Follow-up Most medical conditions leading to peripheral edema are chronic and require long-term follow-up. In these cases, it is particularly important to involve patients in their own health care. Routinely inquire about adherence to medication regimens, and ask patients what they understand about their disease. For the long term, instruct them to monitor their symptoms at home and to chart their weight, an objective way to assess ongoing treatment success or failure. □

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