

A guide to peripheral oedema

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Peripheral oedema is a nonspecific symptom with a wide range of potential causes. A systematic time-efficient review of the patient will aid in differentiating the benign from the more serious causes, guide initial investigations and determine who can be managed in the community and who requires specialist referral or hospitalisation.

KEY POINTS

- The differential diagnosis of peripheral oedema is wide, requiring a systematic approach for diagnosis and management.
- Initial assessment of whether the oedema is generalised or localised is essential to tailor the differential diagnosis.
- Patients whose condition is stable with localised disease processes can be investigated and managed in the community.
- Patients with signs of advanced heart failure or of hepatic or renal disease require early specialist involvement or hospital admission.
- Constrictive pericarditis is a medical emergency that can present with peripheral oedema. A high index of suspicion is required and patients with suggestive signs should be referred for urgent cardiologist review.

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Peripheral oedema is a nonspecific finding common to a wide range of medical conditions and can therefore pose a diagnostic challenge. The causes range from benign conditions that can be managed in the community to major organ failure requiring specialist referral or hospitalisation. A systematic review of the patient and rational, cost-effective investigations are recommended as initial steps in management.

Here we outline conditions that can cause peripheral oedema, details of history taking and examination, and baseline investigations aimed at refining the differential diagnosis and guiding management and referral.

Physiological mechanisms of peripheral oedema

Peripheral oedema is most commonly caused by extravasation of fluid from the vasculature into the interstitium as a result of altered vascular haemodynamics. Starling described the physiological mechanisms causing peripheral oedema as:¹

- increased intravascular hydrostatic pressure
- decreased intravascular or plasma oncotic (colloid osmotic) pressure
- increased vascular permeability.

Any one or more of these factors can underlie peripheral oedema (Figure 1).² Other important causes of peripheral oedema include:

- impaired lymphatic flow
- pregnancy
- physiological changes, such as cyclical premenstrual changes.

Causes of peripheral oedema

Conditions that are associated with generalised or localised peripheral oedema are summarised in Figure 2.

Generalised peripheral oedema

Heart failure

Heart failure is a common and serious cause of generalised peripheral oedema (Figure 3). Left heart failure – either systolic or diastolic – can cause pulmonary oedema, giving rise to dyspnoea. Right heart failure causes peripheral oedema, pleural effusions and sometimes ascites, which can be exacerbated by severe tricuspid regurgitation.

In heart failure, the inability of the heart to effectively circulate blood volume throughout the body leads to increased venous pressure that is transmitted to the capillaries. This causes extravasation of electrolytes and fluid into the interstitium, producing oedema. A low-output state and hypoperfusion of vital organs lead to neurohormonal activation, which aims to restore circulatory homeostasis but in effect worsens cardiac failure and exacerbates oedema. Neurohormonal activation includes stimulation of the sympathetic nervous system, which leads to peripheral vasoconstriction and increases cardiac inotropy and chronotropy, thereby increasing afterload and cardiac work. The release of additional neurohormones of the renin–angiotensin–aldosterone system causes sodium and water retention, while arginine vasopressin (AVP) causes further water retention and peripheral vasoconstriction.

The natriuretic peptides, atrial (ANP) and B-type (BNP), are markers of atrial and ventricular distension and are elevated in heart failure. Serum BNP levels can therefore be used to determine whether heart failure is the cause of peripheral oedema.

Constrictive pericarditis and restrictive cardiomyopathy

Constrictive pericarditis and restrictive cardiomyopathy are less common causes

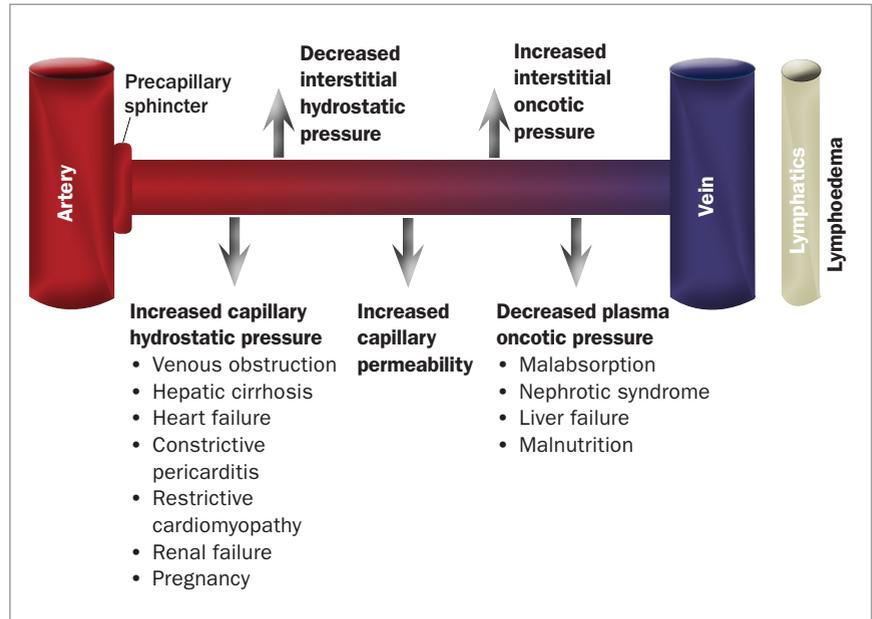


Figure 1. Changes in vascular haemodynamics underlying peripheral oedema.

Adapted from Cho S. Am J Med 2002; 113: 580-586.²

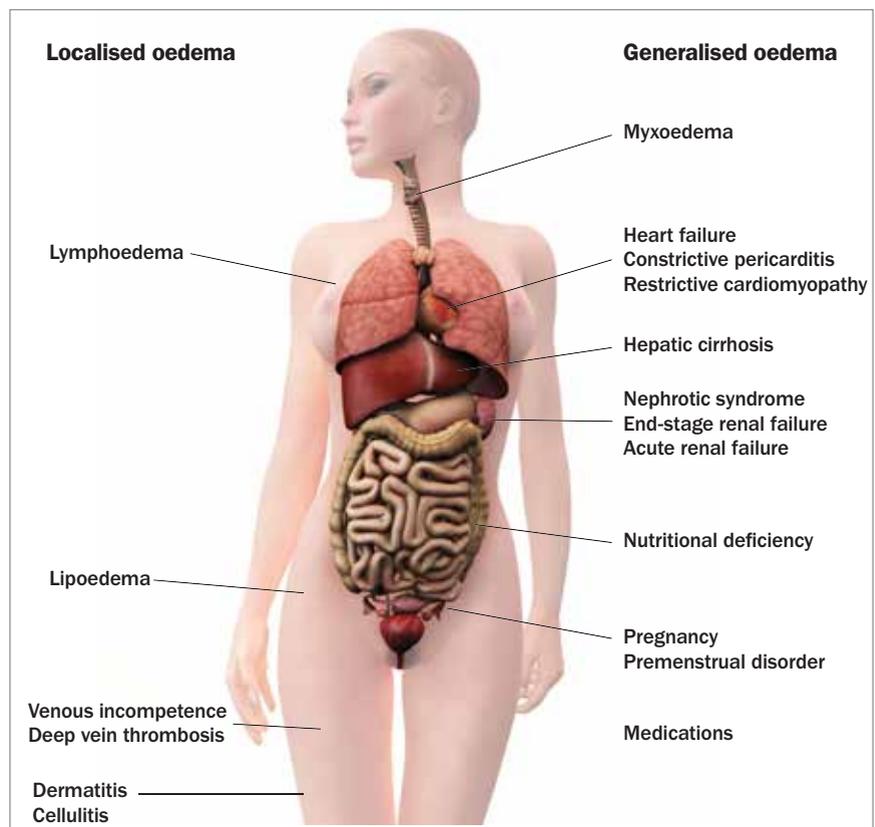
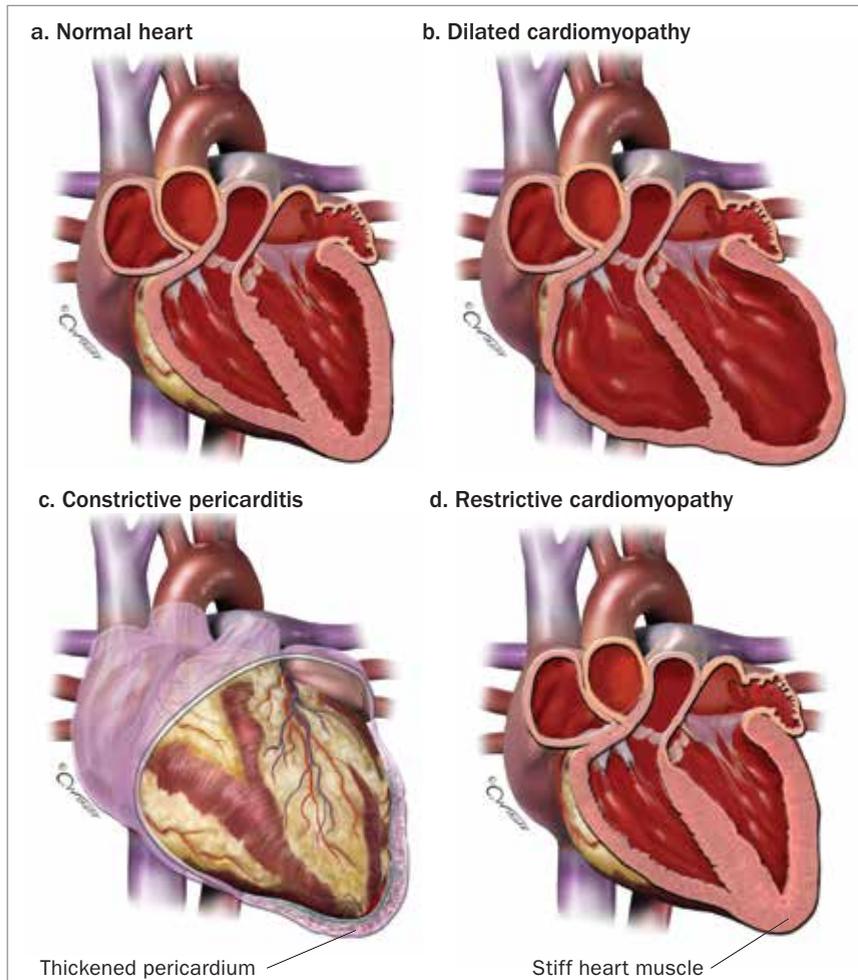


Figure 2. Causes of generalised and localised peripheral oedema.



Figures 3a to d. Cardiac conditions that can cause peripheral oedema. a. Healthy heart. b. Dilated cardiomyopathy with poor systolic and diastolic function of the heart, causing peripheral oedema. c. Constrictive pericarditis causing impaired venous return. d. Restrictive cardiomyopathy causing impaired relaxation of the heart and diastolic heart failure.

of peripheral oedema but are important differential diagnoses to consider (Figure 3). Patients with either of these conditions present with dyspnoea and elevated jugular venous pressure and often have signs of hepatic congestion and ascites as well as peripheral oedema. Echocardiography usually shows normal left ventricular systolic function, but Doppler readings can be used to diagnose pericardial constriction or restriction.

In Australia, the more common causes of constrictive pericarditis include connective tissue diseases, recurrent acute pericarditis, previous surgery or radiation

therapy, malignancy and idiopathic causes. Worldwide, the most common cause is tuberculosis.

The causes of restrictive cardiomyopathy include:

- infiltrative diseases such as amyloidosis and haemochromatosis
- connective tissue diseases such as scleroderma
- hypertrophic cardiomyopathy.

Both constrictive pericarditis and restrictive cardiomyopathy require imaging and right heart catheterisation for definitive diagnosis.

Constrictive pericarditis can cause

cardiac tamponade, which is a cardiac emergency. If there is any clinical suspicion of tamponade (e.g. dyspnoea, elevated jugular venous pressure and signs of right heart failure) then patients require urgent cardiology referral.

Hepatic cirrhosis

End-stage liver disease predominantly causes ascites, but patients also often present with bipedal oedema. Oedema arises due to:

- severe hypoalbuminaemia
- salt and water retention
- formation of multiple arteriovenous fistulae.

Ascites can be severe, and care is needed when performing paracentesis to prevent sudden fluid shifts. Plasma volume and oncotic pressure should be maintained by administering intravenous 20% concentrated albumin while performing slow paracentesis over a few days.

Renal disease

Nephrotic syndrome, acute renal failure and end-stage renal failure can all give rise to peripheral oedema. Nephrotic syndrome is characterised by peripheral oedema in association with high-level proteinuria, low serum albumin levels and high serum cholesterol levels. Diabetic nephropathy is a common cause of proteinuria in adults. Acute renal failure caused by severe renal insults and end-stage renal failure can be associated with oliguria or anuria accompanied by fluid retention, generalised oedema and elevated central venous pressure.

Medications

Peripheral oedema is a common side effect of medications, including:

- calcium channel blockers (e.g. dihydropyridines such as nifedipine, amlodipine, felodipine and lercanidipine, and nondihydropyridines such as verapamil and diltiazem)
- vasodilators (e.g. minoxidil and less commonly hydralazine)

- NSAIDs
- corticosteroids
- antidepressants
- oestrogens and progestones
- thiazolidinediones (e.g. pioglitazone, rosiglitazone).

The mechanism by which calcium channel blockade causes peripheral oedema is through unopposed arteriolar vasodilatation with continued venular constriction. These effects may be minimised by administering calcium channel blockers at night and co-administering ACE inhibitors or angiotensin receptor antagonists. Diuretics should not be used to treat peripheral oedema caused by medications.

Pregnancy

Peripheral oedema is common in pregnancy and is usually seen in the second and third trimesters. Salt and water are retained to increase plasma volume to meet the increased cardiac output required for the fetus and placenta. Compression of the inferior vena cava and iliac veins can exacerbate peripheral oedema in the later stages of pregnancy.

Cyclical or premenstrual oedema

Generalised oedema is relatively common in women during the premenstrual stage of the menstrual cycle. Premenstrual oedema occurs cyclically in the week preceding menstruation and is a diagnosis of exclusion in women with normal serum albumin levels, no elevation of jugular venous pressure and no evidence of renal, hepatic or cardiac disease.

Thyroid disease

Myxoedema can occur in patients with severe hypothyroidism (e.g. Hashimoto's thyroiditis). Myxoedema is nonpitting and caused by dermatological changes, with deposition of glycosaminoglycans, rather than altered vascular haemodynamics. Pretibial myxoedema can also occur in a minority of patients with Graves' disease and hyperthyroidism. Peripheral oedema can be a feature of

high-output cardiac failure in patients with severe hyperthyroidism.

Severe nutritional deficiency

Peripheral oedema can arise due to low serum albumin and protein levels in conditions such as protein-losing enteropathies, severe nutritional deficiencies (e.g. kwashiorkor, which is uncommon in Australia), severe liver disease and severe heart failure. In severe heart failure, 'cardiac cachexia' can result from low albumin and protein levels caused by malabsorption from an oedematous gastrointestinal tract. A clue to a malnourished state (even in a person who is not thin) is the combination of low albumin level and lymphocytopenia.

Obesity-related oedema

Oedema is a common finding in overweight and obese individuals. The causes are not always clear and can be multifactorial. For example, chronic venous insufficiency, impairment of the lymphatic system as well as impaired cardiac, respiratory or renal function can be found in obesity and can contribute to oedema. Obesity-related oedema should again be a diagnosis of exclusion.

Localised oedema

The causes of localised oedema are also important differential diagnoses in patients presenting with peripheral oedema.

Lymphatic obstruction

In Australia, lymphoedema is most commonly caused by destruction of the local lymph nodes by surgery (e.g. mastectomy with axillary lymph node clearance) or radiotherapy. Worldwide, the more common cause is filariasis. In lymphoedema, the skin has a tethered *peau d'orange* appearance and oedema is commonly, but not always, unilateral.

Venous incompetence or deep vein thrombosis

Venous incompetence or a history of deep vein thrombosis can lead to impaired

venous return. This may present with bilateral peripheral oedema but is often asymmetrical. Acute deep vein thrombosis is associated with unilateral swelling, pain and at times erythema. Varicose veins are a sign of venous incompetence but not necessarily associated with peripheral oedema.

Dermatitis and cellulitis

Localised skin irritation can lead to an inflammatory cell infiltrate activated by inflammatory cytokines, such as tumour necrosis factor alpha and interleukin-8, and increased vascular permeability. This is usually associated with erythema and pruritus; however, dermatitis or eczema occurring bilaterally in the lower extremities can mimic peripheral oedema from other causes. Dermatitis is therefore an important differential diagnosis to keep in mind.

Localised oedema associated with pain and erythema are the presenting features of cellulitis. Patients may also have fever. A history of trauma or pruritus points towards cellulitis as the most likely cause.

Lipoedema

Lipoedema is caused by accumulation of fatty deposits, most commonly in the lower extremities. It can be bilateral and mistaken for lymphoedema or venous incompetence, but is differentiated from them by the absence of pitting and of involvement of the feet.

Patient assessment

Knowledge of the common causes and differential diagnoses of peripheral oedema should aid in formulating a comprehensive yet time-efficient, systematic review of the patient. It is important to exclude the more serious differential diagnoses, such as heart failure, hepatic or renal disease, and in patients with acute localised oedema, deep vein thrombosis.

History

Points to cover in history taking in a patient with peripheral oedema are listed in the

HISTORY TAKING IN A PATIENT WITH PERIPHERAL OEDEMA**Current illness**

- Duration of oedema (Is it acute or chronic? Does it improve overnight?)
- Other symptoms
 - dyspnoea
 - oliguria or anuria
 - fatigue, lethargy
 - appetite changes, weight loss
 - pain
 - fever
 - altered mentation
- Pregnancy status, menstrual history (if relevant)

Past history

- Previous episodes of peripheral oedema
- History of systemic or other disease
 - cardiac disease (e.g. heart failure, myocardial infarction, pericarditis, cardiac surgery)
 - hypertension
 - hepatic disease
 - renal disease
 - diabetes
 - thyroid disease
 - connective tissue disease
 - tuberculosis
- History of malignancy, previous radiotherapy or surgery
- History of venous incompetence

Risk factors and family history

- Risk factors for deep vein thrombosis
- Alcohol history
- Family history of heart failure

Medications

- Especially calcium channel blockers, vasodilators, NSAIDs, corticosteroids, antidepressants, oestrogens and progesterones, thiazolidinediones

Box. The presence of dyspnoea points towards a cardiac cause. A history of oliguria or anuria points towards a renal cause but may also be due to severe heart failure. Fatigue, lethargy and changes in appetite accompanying severe generalised oedema suggest advanced cardiac, hepatic or renal disease. Less common causes such as

myxoedema and severe nutritional deficiencies should be kept in mind. Pain and fevers suggest an infective cause such as cellulitis. Altered mentation can point to severe hepatic or renal disease but can also be due to delirium in elderly patients, caused by any of the conditions discussed above.

Physical examination**Distribution of oedema**

Examination of a patient with peripheral oedema should focus initially on the location and distribution of the oedema. Bipedal oedema can be due to any of the causes of generalised oedema discussed above. Unilateral limb oedema can be due to any of the causes of localised oedema, such as lymphoedema, unilateral venous disease, severe dermatitis or cellulitis. Oedema that extends from the lower limbs to involve the scrotum and abdomen indicates advanced cardiac, hepatic or renal disease.

Jugular venous pressure

The jugular venous pressure is the key physical sign in assessing generalised oedema. If the jugular venous pressure is elevated then right heart failure, constrictive pericarditis, restrictive cardiomyopathy and general fluid overload states, such as severe renal dysfunction, should be considered. A normal jugular venous pressure suggests a cause 'below the diaphragm'.

Cardiorespiratory system

A cardiorespiratory examination should be undertaken to detect:

- third or fourth heart sounds
- cardiac murmurs
- crepitations in the lungs
- pleural effusions
- pitting bipedal oedema.

The presence of these signs may indicate heart failure or restrictive cardiomyopathy. Pleural effusions may also occur in the presence of protein-losing states such as nephrotic syndrome or malabsorption.

Constrictive pericarditis should be

considered when a raised jugular venous pressure and dyspnoea are combined with a history of connective tissue disease, recurrent pericarditis, multiple cardiac surgeries, uraemia caused by renal failure or, less commonly in the western world, tuberculosis.

Other signs of systemic disease

The patient should be examined for ascites and jaundice. Patients with hepatic cirrhosis typically have ascites caused by the failure of hepatic synthesis of albumin combined with portal hypertension. Ascites is also common in severe right heart failure.

Oedema caused by thyroid disease is associated with:

- signs of hair loss or coarse hair and sweating (hypothyroidism) or
- ophthalmopathy and features of hyperthyroidism (Graves' disease).

Skin features

Lymphoedema, myxoedema and lipoedema are typically nonpitting. Lipoedema involving the legs typically spares the feet.

A history of pruritus and mild to moderate oedema localised to the legs or arms suggests dermatitis. Erythema and pain on palpation suggest cellulitis but can also be caused by deep vein thrombosis.

Investigations

Investigations should be tailored to the differential diagnosis formulated after history taking and examination. Features of the history that suggest specific diagnoses and suggested investigations are summarised in the Table. Patients who have normal examination results apart from peripheral oedema and are taking a calcium channel blocker or other medication known to cause peripheral oedema may not require investigation but only cessation of the medication and review within a few days. Evidence of cellulitis or dermatitis also warrants treatment without specific immediate investigations.

Conversely, if advanced cardiac, hepatic or renal disease is suspected then referral

TABLE. CAUSES OF PERIPHERAL OEDEMA, SUGGESTIVE FEATURES OF THE HISTORY AND RECOMMENDED INVESTIGATIONS AND REFERRAL

Causes	Suggestive features	Investigations, referral
Generalised peripheral oedema		
Cardiac disease • Systolic heart failure • Restrictive cardiomyopathy • Constrictive pericarditis	History of cardiac disease	Chest x-ray, echocardiography, cardiology referral
Renal disease • Renal failure • Nephrotic syndrome	History of renal disease, diabetes, hypertension	Serum electrolytes, urea and creatinine, lipids Urine protein ± renal tract ultrasound, referral to renal physician
Hepatic disease • Cirrhosis	History of hepatitis, alcohol misuse	Serum albumin, liver function tests, INR, APTT, ± hepatic ultrasound, referral to gastroenterologist
Medication side effects • Calcium channel blockers • Minoxidil • Corticosteroids • Thiazolidinediones • NSAIDs • Hormonal treatment	Medication history	
Thyroid disease	History or symptoms of thyrotoxicosis or hypothyroidism	Serum TSH, free T4 and T3
Pregnancy		
Cyclical (premenstrual)		
Severe nutritional deficiencies	Nutritional history	Serum albumin and protein
Obesity		
Localised peripheral oedema		
DVT	History of risk factors for DVT	Venous ultrasound, dopplers
Venous incompetence		Venous ultrasound, dopplers
Lymphatic obstruction	History of surgery	Lymphoscintogram
Dermatitis	History of allergy, previous dermatitis	
Cellulitis	Localised trauma, pain, tenderness	No specific investigation required before treatment

Abbreviations: APTT=activated partial thromboplastin time; DVT=deep vein thrombosis; INR=international normalised ratio; T3=tri-iodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone.

is warranted for specialist review or to the emergency department, depending on the severity of the presenting symptoms.

Blood and urine tests

Patients presenting with less critical symptoms should undergo investigations, including:

- serum electrolytes, urea and creatinine levels
- liver function tests, including albumin level
- coagulation studies
- full blood count
- blood sugar level
- thyroid-stimulating hormone level
- spot urinalysis, looking for protein and glucose.

Imaging

Pleural effusions or lung crepitations detected on clinical examination warrant a posteroanterior and lateral chest x-ray. These patients should also be referred for echocardiography to assess for the degree of heart failure, valvular disease and gross pericardial abnormalities.

If history or examination findings or initial blood test results suggest renal or hepatic disease then a renal tract or hepatic ultrasound examination, respectively, is warranted.

Patients with a suspected deep vein thrombosis should have a venous ultrasound examination performed on the same day.

B-type natriuretic peptide

Measurement of the BNP level in blood can be valuable in determining whether a patient's symptoms are caused by an exacerbation of heart failure. A significant elevation in BNP associated with increasing dyspnoea can help with the diagnosis in a patient with multiple comorbidities.

Management

For patients with heart failure who do not require immediate hospital admission, treatment can be initiated with oral diuretics such as frusemide and potassium

replacement pending review by a cardiologist. These patients should be advised to restrict fluids and adopt a low salt intake to prevent exacerbations, and to monitor their weight at home to detect early signs of fluid retention.

Patients with constrictive pericarditis or signs of more advanced heart failure (such as a markedly raised jugular venous pressure associated with respiratory distress) require more urgent cardiology referral. Patients who have evidence of renal, hepatic or thyroid disease or nutritional deficiencies but whose condition is stable do not require hospitalisation but should have specialist involvement as early as possible.

Management of patients with localised causes of oedema can be initiated in the community, and the patients reviewed to monitor progress. Treatments include anticoagulation for deep vein thrombosis, elevation for dependent oedema, compression stockings for isolated venous hypertension and antibiotics for cellulitis.

Conclusion

The causes of peripheral oedema are varied, requiring a systematic approach to history taking and examination. Diagnosis is often a process of elimination of the common causes. Most patients who present early can be managed in the community.

Patients with advanced cardiac, hepatic or renal disease with gross peripheral oedema warrant urgent specialist review or hospital admission. A high index of suspicion is required to detect rarer but potentially life-threatening causes of peripheral oedema, such as constrictive pericarditis. **MT**

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