Chronic peripheral oedema and lymphoedema 3811 Pet

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Peter S. Mortimer

ESSENTIALS Lymph transport, not venous reabsorption, is the main process re- sponsible for interstitial fluid drainage. Oedema develops when the microvascular filtration rate exceeds lymph drainage for a suffi- cient period, and any chronic oedema represents a failure of lymph drainage. In practice, any chronic oedema should be managed in the same way as lymphoedema. Causes of lymphoedema Lymph drainage may fail either because of a defect intrinsic to the lymph conducting pathways (primary lymphoedema), or because of irreversible damage from some factor(s) originating from out- side the lymphatic system (secondary lymphoedema). Primary lymphoedema is caused by genetic faults in lymphatic development (e.g. germline mutations in the vascular endothelial growth factor receptor-3 gene which causes Milroy's disease), but in most cases the genetic cause is unknown. Filariasis is by far the most common cause of secondary lymphoedema worldwide. Most cases in the developed world are secondary to cancer treatment, obesity, and poor mobility. Clinical features and management Lymphoedema causes persistent swelling often associated with recur- rent cellulitis. It should be managed clinically by considering reasons for impaired lymph drainage and reasons for high lymph load (e.g. high venous pressures including heart failure, hypoproteinaemia, and inflammation). The investigation of choice for confirmation of diagnosis is lymphoscintigraphy. No drug is known to improve lymph drainage. Diuretics should only be considered for high lymph loads. Current best practice aims to (1) improve lymph drainage through physiological principles known to stimulate lymph flow (i.e. exercise and movement combined with compression); and (2) control any high lymph load. Recurrent cellulitis is common, with each attack causing fur- ther decline in lymph drainage and worse swelling. Prevention and prompt treatment are crucial to the control of lymphoedema. Introduction The primary function of the lymphatic vessels is to drain the plasma filtrate within body tissues and return it to the blood circu- lation. Lymphatic vessels also have an important immune surveil- lance function, as they are the main drainage route from the tissues for immune active cells such as

dendritic cells, lymphocytes, and macrophages. Intestinal lymphatics are responsible for fat absorp- tion. Impaired lymphatic function leads to disturbed fluid homeo- stasis (swelling), dampened immune responses (infection), and disturbed fat homeostasis (increased peripheral fat deposition), all features of lymphoedema. Lymphatic vessels are also the preferen- tial route for cancer spread. Oedema Oedema is an excess of interstitial fluid and is an important sign of ill health in clinical medicine. The usual clinical approach to peripheral oedema is to consider a single diagnosis such as heart failure, nephrotic syndrome, venous obstruction, or lymphoedema. This viewpoint fails to appreciate the many dynamic physiological forces contributing to oedema development and in particular the central role of the lymphatic drainage system in tissue fluid (and consequently plasma volume) homeostasis. Hence the clinician's ap- proach to peripheral oedema is often misguided and the necessary medical intervention inappropriate (e.g. empirical use of diuretics). Management of peripheral oedema is better based on physiological principles that can then guide treatment. Pathophysiology Lymph transport, not venous reabsorption, is the main process re- sponsible for interstitial fluid drainage. Oedema develops when the microvascular (from capillaries and venules) filtration rate exceeds lymph drainage for a sufficient period, either because the filtration rate is high (high lymph load) or because lymph flow is weak, or a combination of the two. Filtration rate is governed by the Starling 16.18 Chronic peripheral oedema and lymphoedema Peter S. Mortimer

section 16 Cardiovascular disorders 3812 principle of fluid exchange, which is described succinctly and quan- titatively by the Starling equation for flow across a semipermeable

membrane (Fig. 16.18.1). In simple terms, filtration of fluid from capillary into interstitium is driven by the hydraulic (water) pressure gradient across the wall (Pc − Pi) and is opposed by the osmotic pressure gradient (πp − πi), which is the ‘suction’ force keeping fluid in the circulation. The Starling equation provides a logical approach for

classifying oedema that is due to increased filtration (Box 16.18.1) Traditionally it has been taught that the arterial end of capillaries filters fluid while the venous end reabsorbs the bulk of fluid filtered. This view is not supported by modern evidence, which demonstrates that in most vascular beds there is a net but dwindling filtration along

the entire length of well-perfused capillaries. The sum of all Starling forces is not an absorptive force in venous capillaries but a slight fil- tration force (except following haemorrhage, for example, when ca- pillary pressure drops sufficiently for transient absorption to occur). Even under such circumstances Starling

forces soon re-equilibrate and slight filtration is restored. Sustained reabsorption of fluid is a normal feature of some microcirculatory beds, namely intestinal mucosa, renal peritubular, and lymph node capillaries, but not peripheral tissues. Since the old concept of sustained fluid absorption by venous capillaries is no longer

tenable, the major responsibility for drainage of interstitial fluid is through the lymphatic system.
Restraining factors against oedema include
(1) elevation of inter- stitial fluid pressure, (2) fall in interstitial colloid osmotic pressure (COP), and (3) increased lymph flow.
Stiffness in tissues resists swelling. A small increase in

interstitial fluid in a stiff tissue (low compliance) will cause a relatively large increase in interstitial pres- sure (Pi), which then opposes filtration. Placing a bandage or rigid stocking around a leg will reduce compliance by effectively increasing stiffness. Consequently, Pi will increase more steeply for a given inter- stitial volume

increase and the increased Pi will oppose filtration. Relating to interstitial COP, an increase in filtration rate will dilute the interstitial protein concentration and consequently reduce the osmotic pressure (π immediately outside the semipermeable mem-brane). The resulting increase in the osmotic pressure gradient will raise

the suction force keeping fluid within the blood compartment. Increases in interstitial fluid pressure and volume stimulate lymph flow. Lymph drainage is a complex process involving absorption of protein and fluid (as well as other macromolecules, microorgan- isms, immune cells, and cancer cells) from the interstitium into initial

lymphatic vessels (also known as lymphatics) and then down- stream through vessels of ever-enlarging diameter until reaching the main collecting lymphatics that pump lymph to the sentinel lymph nodes. Valves ensure unidirectional flow. Transport of interstitial fluid into and along initial lymphatics is largely a passive process L dv

dt V – J J L (net capillary filtration rate) (rate of swelling) (Lymph flow) JV = S σ } (p– i) Starling force Mechanism Starling equation (Pc – Pi) { Interstitial osmotic pressure Raised with increased permeability i.e. water follows protein-altered in inflammation Plasma osmotic pressure Reduced in hypoproteinaemia- protein losing states e.g. nephrotic syndrome, malnutrition, or a failure of hepatic protein synthesis e.g. cirrhosis Ability of capillary to 'reflect' or hold protein in circula- tion-altered in inflammation Osmotic reflection coefficient Interstitial pressure Raised in oedema, lowered if compliance of tissues increases e.g. lax skin Capillary pressure Raised predominantly by venous pressure- altered in heart failure, venous obstruction, fluid retention e.g. secondary hyperaldo- steronism Surface area of capillary Influenced by capillary density and length of capillaries such as in angiogenesis, and vasodilatation e.g. inflammation Hydraulic conductance Ease of passage of fluid across capillary wall- altered in inflammation π π Fig. 16.18.1 Physiology of oedema. Box 16.18.1 Starling forces in the classification of oedema 1 Raised capillary pressure Capillary pressure is more susceptible to changes in venous pressure than systemic (arterial) blood pressure because postcapillary resistance is much lower than precapillary resistance. Peripheral venous pressure is raised in: • right ventricular failure • salt and water overload (e.g. overtransfusion) • venous obstruction • venous reflux (chronic venous disease), e.g. following deep vein thrombosis, primary varicose veins • dependency (the effect of gravity) 2 Reduced plasma osmotic pressure (COP) • This essentially means hypoalbuminaemia, which can arise from: • malnutrition • intestinal disease (malabsorption or protein loss) • nephrotic syndrome • hepatic failure to synthesize albumin—due to liver disease or chronic inflammatory states 3 Increased capillary permeability Inflammation can cause a breakdown in the endothelial barrier, facilitating the passage of both plasma proteins and water across the ca- pillary wall. In addition, vasodilatation causes a rise in capillary pressure (and blood flow).

16.18 Chronic peripheral oedema and lymphoedema 3813 dependent upon changes in tissue (interstitial) pressure from move- ment (active and passive exercise), massage, and local arterial pulsa- tion and—in more central tissues—breathing. The larger collecting lymphatics contract and are mainly responsible for pumping lymph against gravity. Successive segments of collecting lymphatics be- have like 'mini hearts' in series, and their contractile cycle bears striking similarities to the cardiac cycle. Sympathetic input influ- ences the pumping rate, while the diastolic filling (preload or supply from upstream lymphatics) controls the force of contraction. Flow in collecting lymphatics is only as good as the supply from initial (noncontractile) lymphatics. Influx of calcium ions is important for smooth muscle contraction in the walls of the collecting lymphatics, hence calcium channel antagonists may cause oedema by paralysing lymphatic pumping. The lymph vessels return the capillary filtrate back to the blood- stream via the lymph nodes and eventually the thoracic duct. This completes the extravascular circulation of fluid and protein and maintains tissue volume homeostasis. Lymph flow should respond to increases in capillary filtration and so prevent oedema. By failing to compensate for increased capillary filtration and so permit swelling, the lymphatic is to some extent failing in its duty to preventing all types of oedema. Differences in lymph drainage capacity could be the explanation for differing levels of leg oedema seen in patients with right-sided heart failure despite no difference in ejection frac- tion. Similarly, peripheral oedema that persists after heart failure has been successfully treated is likely to be lymphatic in origin. True lymphoedema is strictly oedema arising from reduced lymph transport that is unable to cope with normal levels of capil- lary filtration. Most oedema arises from increased capillary filtra- tion (high lymph load) overwhelming lymph transport capacity for a sustained period of time. Once high lymph flow cannot be sus- tained and transport capacity fails, 'true'

lymphoedema ensues. This pathophysiology is comparable with that occurring in high-output cardiac failure. Aetiology Lymph drainage may fail either because of a defect intrinsic to the lymph conducting pathways (primary lymphoedema, Figs. 16.18.2a and 16.18.2b) or because of irreversible damage from some factor(s) originating from outside the lymphatic system (secondary lymphoedema, Fig. 16.18.2c). Physiologically there are only a limited number of ways that lymphatics can fail. They may be reduced in number (aplasia/ hypoplasia), obliterated or damaged without repair (failed lymphangiogenesis), or obstructed; they may lose contractility (pump failure), or become incompetent (valvular reflux). A lack of sensitive methods for investigation makes it difficult to dis- tinguish between these mechanisms. Primary lymphoedema Primary lymphoedema arises from an inborn, or intrinsic, fault in lymphatic vessel architecture, function, or both, and by implica- tion is genetic in origin. Lymphoedema is seen in many syndromes, including Turner and Noonan syndromes, but as an associated fea- ture and not the main manifestation. A defining moment in lymphatic research came with the dis- covery of the receptor vascular endothelial growth factor receptor- 3 (VEGFR-3) and its ligands VEGF-C and VEGF-D as the main signalling mechanism for lymphangiogenesis. Historically, all cases of congenital lymphoedema were classified as Milroy disease, but Fig. 16.18.2 (a) Causes of primary lymphoedema. (b) Classification and diagnostic algorithm for primary lymphatic dysplasia. (c) Causes of secondary lymphoedema. Part (b) is adapted from Connell F, et al. (2013). The classification and diagnostic algorithm for primary lymphatic dysplasia:
an update from 2010 to include molecular findings. Clin Genet, 84, 3031–4, Copyright © 2013, John Wiley and Sons.

 Multiple segments No Yes Disturbed growth/ cutaneous manifestations/ vascular anomalies Unknown syndrome Known syndrome SOX18, e.g. Noonan and Turner Yes Start No No Syndromic Systemic/visceral involvement pre- or postnatal onset Generalized lymphatic dysplasia (GLD)/ Hennekam syndrome Consider CCBE1, FAT4, PIEZO1 Lymphatic-related hydrops fetalis (LRHF) Consider PIEZO1, EPHB4 Multisegmental lymphatic dysplasia with systemic involvement (MLDSI) Yes Some segments All segments Bilateral One limb No No No Lower limbs only Distichiasis Lymphoedema-distichiasis syndrome FOXC2 Late-onset unilateral leg lymphoedema Meige-like Meige Consider GJC2 Late-onset unisegmental lymphoedema Late-onset multisegmental lymphoedema Late-onset lower limbs ± genitalia Consider GATA2 4-limb Consider GJC2, Turner Bilateral Unilateral FH +ve FH –ve Yes Yes Congenital onset (<1 y) Late onset (>1 y) Unilateral FH –ve Lower limb + genitalia Much of the improved knowledge about lymphatic science has come from investigating mouse models, but knowledge of genetic causes has come from human studies. Identification of genes underlying primary lymphoedema has also led to greatly enhanced knowledge of lymphangiogenesis as a result of investigating previously unrecognised pathways (e.g. SOX18, FOXC2, CCBE1 and VEGFR3). We also believe that the discovery of genes important for lymphatic development may help in the understanding of diseases where lymphatic dysfunction is known to play a part, e.g. Crohn’s disease. Lower limb FH +ve Proteus syndrome AKT1 (b) PIK3CA-related overgrowth spectrum (PROS) • CLOVES • Fibroadipose hyperplasia • KTS / KT-like • Lymphatic malformation • Combined vascular malformation PIK3CA Parkes-Weber syndrome RASA1 Progressive lymphangiomastosis Gorham syndrome Generalized lymphatic anomaly WILD syndrome Congenital multisegmental oedema without systemic involvement Congenital unisegmental oedema Congenital lower limb oedema with reflux and rerouting Milroy disease FLT4 (VEGFR3) Milroy-like Consider KIF11, VEGFC Congenital lower limb

- genital oedema Consider PIEZO1 Fig. 16.18.2 Continued

16.18 Chronic peripheral oedema and lymphoedema 3815 several different types of congenital lower limb primary lymphoedema are now recognized. They may all look clinically similar at birth, and only with genetic testing can they be distinguished from one another. For example, mutations in VEGFR3, VEGFC, and KIF11 can all present with exactly the same type of lymphoedema at birth. Mutations in the gene VEGFR-3 are the cause of congenital fa- milial lymphoedema (Milroy disease). The phenotype manifests with inheritable lymphoedema at or soon after birth, with swelling confined to one or both feet and ankles due to impaired function of initial lymphatics. A phenotype similar to Milroy and also occurring from birth or within the first year is microcephaly lymphoedema syndrome, for which the mutation is in KIF11, hence it is important to measure head circumference in congenital lymphoedema con- fined to the feet and legs. A widespread developmental abnormality of the lymphatic system leads to systemic/visceral involvement and swelling that may not be confined to the limbs (generalized lymphatic dysplasia). Lymphatic dysfunction may present prenatally with hydrothoraces, ascites, or hydrops fetalis. The development of in-utero oedema may cause dysmorphic facial features such as epicanthic folds, a broad nasal bridge, and neck webbing with low-set ears. Primary lymphoedema may be sporadic and involve several limbs, genitalia, or even the face (multisegmental). A failure in lymphatic development may also manifest with internal lymphatic abnormalities such as pleural/peri- cardial effusions, and pulmonary or intestinal lymphangiectasia. Intestinal lymphangiectasia, or disturbances in mesenteric lymph drainage, may result in chylous reflux, with chyle rerouting to various parts of the body (e.g. chylous effusion or ascites). The fat as well as protein content of such fluids should be measured for diag- nosis. Intestinal lymphangiectasia will cause a protein losing enter- opathy which will result in hypoalbuminaemia, which will make any existing lymphoedema worse by increasing microvascular fluid filtration. Four genes are currently known to cause lymphoedema with sys- temic lymphatic abnormalities: CCBE1, FAT4, PIEZO1, and EPHB4. Generalized lymphatic dysplasia due to CCBE1 or FAT4 (Hennekam syndrome) is autosomal recessive and presents with lymphoedema of all four limbs, intestinal, and/or pulmonary lymphatic dys- plasia, a variable degree of learning difficulties, and characteristic facies. Mutations in PIEZO1 result in a high incidence of non- immune hydrops fetalis and childhood onset of facial and four limb lymphoedema. The term late-onset lymphoedema is used to describe a primary lymphoedema that develops after the first year of life (i.e. non- congenital lymphoedema). Some of these forms of lymphoedema have life-threatening-associated diseases, but they all share the common finding of non-congenital limb swelling. Emberger’s syn- drome, caused by mutations in the transcription factor GATA2, manifests with myelodysplasia which predisposes to acute mye- loid leukaemia. Systemic immunodeficiency is another associated feature, indicating the close relationship between the lymphatic system and immune competence. Mutations in FOXC2 cause lymphoedema–distichiasis, a dominantly inherited late-onset (postpubertal) lymphoedema associated with a double row of (ingrowing) eyelashes (distichiasis) and varicose veins. A defect in lymphatic valves results in lymph reflux. Swelling may not mani- fest until the fifth decade, indicating how genetic abnormalities can cause late-onset lymphoedema. The phenotype can also cause congenital heart disease, emphasizing the close relationship be- tween cardiovascular and lymphatic development. For most forms of primary lymphoedema the genetic cause re- mains unknown. Familial forms with a reduction in size and number of superficial lymphatic collecting vessels but no other phenotypic features are called Meige’s disease. Lymphoedema of the proximal obstructive type with unilateral whole-limb swelling is sporadic in type, with lymphangiograms

demonstrating obstruction at the inguinal nodes, so called ilio-inguinal nodal sclerosis, with no apparent cause. In cases of proximal obstruction, it is of the utmost importance to exclude tumour or iliac vein thrombosis. Asymmetrical primary lymphoedema associated with tissue overgrowth with, or without, a vascular birthmark is often caused by a somatic mutation. These mosaic disorders develop mutations during embryonic development after fertilization, and so are gener- ally not inherited. Cases of unilateral limb swelling associated with overgrowth and a port wine stain and/or varicose veins are often caused by somatic mutations in the PI3K-AKT-MTOR pathway and as such are known as PIK3CA-related overgrowth spectrum or PROS. Certain lymphatic malformations and Klippel–Trenaunay syndrome develop through this mechanism. Proteus syndrome caused by mutations in the AKT pathway is related. The yellow nail syndrome, although given an OMIM number, rarely has a family history and is of unknown cause. It is diagnosed when at least two out of three associated clinical features are pre- sent, namely discoloured yellow, thickened, and slow-growing nails; lymphoedema; and respiratory disease such as bronchiectasis, pleural effusions, or chronic sinusitis. Secondary lymphoedema Filariasis is by far the most common cause of lymphoedema world- wide (filarial elephantiasis). It is endemic in eastern Asia, the Indian subcontinent, west and east Africa, Brazil, and the Caribbean. Microfilaria introduced into the skin by mosquitoes migrate to- wards and enter initial lymphatics. Adult worms develop within the main collector vessels close to the nodes, resulting in lymphatic dila- tation and lymphadenitis. Podoconiosis (endemic elephantiasis) is a form of endemic non- filarial lymphoedema caused by microparticles of silica that pene- trate the feet during barefoot walking in soil containing silica and aluminosilicates in tropical west and east Africa, certain volcanic islands, and Central America (see Chapter 10.5). The skin changes are often gross with minimal pitting oedema. There may be a genetic predisposition. In developed countries, surgical removal or irradiation (or both) of lymph nodes for cancer treatment results in lymphoedema. In breast-cancer-related lymphoedema the exact mechanisms for de- velopment are unclear, but evidence suggests a simple ‘stopcock’ obstruction from scarring in the axilla is unlikely. Lymphoedema can develop in some patients after removal of one (sentinel) node, but not in others who have had a complete axillary clearance. The incidence of arm lymphoedema remains stubbornly high at over 1 in 5 despite developments such as breast-conserving surgery and sentinel lymph node biopsy. Obesity is a strong risk factor for the condition, as it is for all types of lymphoedema, and weight loss has been shown to improve existing lymphoedema significantly. The use of taxanes in chemotherapy appears to be contributing to breast-cancer-related lymphoedema. Cancer rarely presents with

 lymphoedema, except in advanced disease, but relapsed tumour fre- quently results in lymphoedema due to obstruction or infiltration of collateral lymphatic routes that have hitherto permitted escape of lymph. Kaposi’s sarcoma is thought to arise from human herpesvirus- 8-induced reprogramming of lymphatic endothelial cells. Vascular plaques in skin and lymphoedema characterize Kaposi’s sarcoma. Lymphangiosarcoma is a highly malignant tumour of endothelial cells which usually arises in long-standing lymphoedema. Sustained periods of high lymph load (increased micro- vascular filtration) from venous hypertension due to heart failure or venous disease will overwhelm and then eventually exhaust lymph drainage capacity so that permanent impairment of lymph drainage results. A good example is right-sided heart failure. Peripheral oedema results from a high lymph load overwhelming lymph drainage. If the oedema does not resolve when the heart failure is controlled (and lymph load normalized), an exhausted and permanently weakened lymph drainage (i.e. lymphoedema), is one likely explanation. Obesity is increasingly recognized as a risk factor for lymphoedema. It impairs lymph drainage, which in

turn causes deposition of per- ipheral subcutaneous fat, excess fat (as well as fluid) being one of the main tissue components contributing to the swelling in a breast- cancer-related lymphoedema arm. Morbidly obese patients will often have other comorbidities contributing to leg lymphoedema, including poor movement and a lack of exercise. Long periods sit- ting with legs dependent increase lymph load. Lymphangitis or cellulitis probably only causes lymphoedema when the lymphatics are perilously vulnerable. Any patient suffering recurrent lymphangitis/cellulitis in the same region is likely to have pre-existing impaired lymphatic function. Recurrent attacks of cel- lulitis frequently lead to a stepwise deterioration in swelling. Functional leg lymphoedema may develop as a result of immo- bility and dependency due to infirmity following stroke, severe arth- ritis, or respiratory disease, with long periods spent in a chair. It is the lack of exercise which results in no stimulation of lymph drainage. Lymphoedema is a common consequence of post- thrombotic syndrome (following deep vein thrombosis) and severe long- standing venous reflux due to varicose veins. High filtration rates from the ambulatory venous hypertension slowly exhaust lymph drainage. Irreversibly impaired lymph drainage eventually results. Lymphoedema can also result from long-term inflammatory states such as rheumatoid arthritis and chronic hand or foot dermatitis (with or without infection). Drug treatment can cause or contribute to lower limb lymphoedema. The most common culprits are calcium channel ant- agonists, which are known to paralyse lymphatic vessel pumping, but an increase in lymph load may also be a factor. The incidence and severity of oedema varies between agents, with amlodipine being one of the worst. Other drugs reported to cause oedema include steroids, taxanes, pramipexole, cabergoline, NSAIDs, pregabalin, olanzapine, thiazolidinediones, quetiapine and pemetrexed (eyelid oedema). Epidemiology An estimated 15 million people suffer from leg lymphoedema in filariasis-endemic areas of the world. Other lymphatic manifest- ations such as genital lymphoedema and hydrocoele are equally common. Lymphoedema due to podoconiosis is estimated to af- fect approximately 4 million people, with the greatest numbers in Ethiopia. In the United Kingdom, secondary forms of lymphoedema, par- ticularly cancer-related lymphoedema, are most frequent. More than one in five women who survive breast cancer will develop arm lymphoedema. Other cancers such as cervix, uterus, vulva, prostate, penis, head and neck, melanoma, and sarcoma are commonly asso- ciated with lymphoedema as a result of treatment or through pro- gressive disease. Attempts to determine the prevalence of lymphoedema in the general population are sparse, and most previous studies have re- lied on information that has been obtained from specific patient groups such as those with breast cancer. A recent epidemiological study of community patients revealed a point prevalence that was much higher among women than men (5.37 vs. 248/1000 popula- tion). It was also more prevalent among the obese, and there was a clear rise in prevalence with increasing age. The prevalence among hospital inpatients was a staggering 28.5%, which was not the reason for admission but highlights that lymphoedema frequently coexists with other morbidities. Prevention Identification of patients at risk of lymphoedema relies on awareness of its causes. In breast cancer the strongest risk factors are obesity, stage of cancer, extent of surgery, and postoperative infection. In fil- ariasis and podoconiosis avoidance of infection through good skin and foot care seems the most important aspect of care for preventing elephantiasis changes. Clinical features Painless swelling that develops in the wake of cancer treatment is likely to be lymphoedema. Primary lymphoedema is rarely con- sidered at presentation and consequently diagnosis is usually de- layed while other possible causes of swelling are investigated and excluded. Lymphoedema most commonly affects the extremities, particu- larly the leg, although midline swelling affecting head and neck or genitalia can be an isolated finding. Truncal oedema is often observed in the adjoining quadrant of the trunk to an affected limb because of the shared

lymph routes within the same lymph drainage basin. Oedema that is symmetrical (equal between right and left legs) is more likely to have systemic origins (e.g. right- sided heart failure or hypoproteinaemia). Oedema that is asym- metrical (more in one leg than the other) implies a local cause (e.g. impaired venous or lymph drainage, but both systemic and local causes can coexist). In a patient with advanced cancer leg oedema may result from a combination of hypoproteinaemia (liver metas- tases), impaired lymph drainage (original lymphadenectomy and/ or lymphatic infiltration by tumour), venous obstruction (deep vein thrombosis or vein compression by tumour), immobility, and dependency. History Leg swelling frequently develops rapidly—within a day—but may be mild and intermittent at first. Pain may feature initially, prompting diagnoses such as deep vein thrombosis, soft tissue injury, or infec- tion (although cellulitis often triggers lymphoedema).

16.18 Chronic peripheral oedema and lymphoedema 3817 No oedema is normal. Foot or ankle swelling that regularly occurs on long haul flights, with prolonged standing or in heat, suggests that lymph drainage is not robust. Indeed, it is not unusual for a patient with primary lymphoedema to experience such symptoms for some years before, eventually, more permanent swelling ensues. Discomfort, aching, and heaviness are common symptoms. Functional impairment is slight until swelling becomes more se- vere (Fig. 16.18.3). Lymphoedema does not respond much to elevation or diuretics, except in the early stages or when it is compounded by increased capillary filtration (high lymph load). Chronic oedema that does not reduce significantly overnight is likely to be lymphatic in origin. Clinical signs It is often said that lymphoedema does not pit, but this is not true unless the advanced stages of fibrosis (elephantiasis) have been established. To demonstrate pitting in lymphoedema sustained pressure for some 20 s may be necessary, owing to the firmer (and thicker) nature of the skin and subcutaneous tissues. The skin may double in thickness in lymphoedema, particularly at the base of the second toe, where it may become impossible to pinch up a fold of skin. An inability to pinch and lift a fold of skin at the base of the second toe is referred to as the (Kaposi–) Stemmer sign and is pathognomonic of lymphoedema (Fig. 16.18.4, Table 16.18.1). As the skin thickens so creases become enhanced and a warty texture (hyperkeratosis) develops. Accumulation of lymph under pressure in dermal lymphatics can result in lymph blisters that bulge on the surface (lymphangiectasia) and weep lymph. When associated with dermal fibrosis the surface bulges are firmer and resemble cobblestones (papillomatosis). The resemblance of the skin texture to elephant hide explains the term elephantiasis (as well as having a leg the size of an elephant’s leg). Intestinal lymph that is rerouted or refluxes into more dependent re- gions of the body will appear milky (chyle) due to its high fat con- tent. Chyle may reflux into the lower limbs, genitalia, peritoneal cavity, urinary and genital tracts, pleural cavity, and other cavities such as synovial joints and pericardium. Chyle will only appear if the lymphatic incompetence extends up to the preaortic lymphatics and cisterna chyli. Cellulitis (erysipelas) In addition to swelling, impaired lymph drainage also predis- poses to infection because of the role the lymphatic system plays in immunosurveillance. Episodes of cellulitis or erysipelas can often be recurrent and frequent. Such events occur irrespective of the cause of the lymphoedema, and covert lymphoedema should be con- sidered as a possible cause in patients presenting with acute cellu- litis, particularly if attacks are recurrent. In filarial lymphoedema, where the episodes of infection are called acute dermato-lymphangio-adenitis, these secondary bacterial Fig. 16.18.3 Lymphoedema exhibiting characteristic skin changes (thickened skin with warty surface change and in more advanced cases ‘cobblestone’ papillomatosis) together with loss of shape and folds developing around the ankles. Fig. 16.18.4 Kaposi–Stemmer sign: the inability to pinch and pick up a fold of skin at the base of the second toe (due to thickened skin). Table 16.18.1 Criteria

for diagnosis of lymphoedema Symptoms Persistent swelling (can be intermittent at first) Oedema does not resolve with overnight elevation Poor response to diuretics Associated with cellulitis Signs Pitting oedema (but difficult to pit) Thickened, warty skin Kaposi–Stemmer sign Investigation Abnormal lymph drainage routes or impaired transport
on lymphoscintigraphy

section 16 Cardiovascular disorders 3818 infections appear to be important for the progression of the ele- phantiasis. They manifest with increased oedema, pain, fever, or flu-like symptoms, and can be prevented with long-term penicillin and improvements in skin hygiene. In primary and cancer-related lymphoedema recurrent cellulitis can be as common as in filariasis, suggesting that disturbed immune cell trafficking associated with the lymphoedema is the fundamental cause. Differential diagnosis of the swollen limb Both excessive capillary filtration and compromised lymph drainage frequently coexist (Fig. 16.18.5). ‘Venous’ oedema Most cases of chronic venous disease giving rise to venous hyper- tension do not manifest with oedema because of increased lymph flow in response to increased capillary filtration. This suggests that the development of oedema in post-thrombotic syndrome and venous ulceration is as much a failure of lymph drainage as it is due solely to overwhelming microvascular fluid filtration (high lymph load). Correction of the superficial vein incompetence by surgery may not resolve the oedema because of coexistent and permanent lymphatic insufficiency. Lipodermatosclerosis Chronic ‘congestion’ in the lower leg resulting from both in- creased capillary filtration and impaired lymph drainage will often result in lipodermatosclerosis. This manifests with skin red- ness, induration of underlying subcutaneous tissues, tenderness, and oedema. It is usually seen just above the medial malleolus or anterior gaiter region (Fig. 16.18.6). Lipodermatosclerosis is reported to occur with venous disease but it can frequently be seen with lymphoedema in the absence of venous disease. It is frequently mistaken for cellulitis but antibiotics have little effect. Only ‘decongestion’ through compression or elevation improves the condition. ‘Armchair’ legs (dependency syndrome) This syndrome refers to those patients who sit in a chair day and night with their legs dependent. Immobility results in minimal lymph drainage and ‘functional lymphoedema’ ensues (i.e. there is no stimulation of lymph drainage from movement). The asso- ciated increased capillary filtration from gravitational forces leads to profound lower limb oedema. Patients predisposed are those suffering cardiac or respiratory failure who cannot lie flat, those paralysed from stroke or spinal damage including spina bifida, and those with crippling arthritis, particularly rheumatoid. Becoming more common with this scenario are excessively obese individuals with or without obstructive sleep apnoea. Lipoedema (lipodystrophy, lipohypertrophy, lipidosis) Frequently misdiagnosed as lymphoedema, lipoedema is almost exclusive to females with onset at or after puberty. Lipoedema (lip = fat, oedema = swelling) results in excessive fat deposition below the waist (and sometimes upper arms), but not affecting the Fig. 16.18.5 Causes of a chronically swollen limb. Fig. 16.18.6 Lipodermatosclerosis, a consequence of chronic congestion, manifests with fixed plum-red discolouration of skin, subcutaneous induration, and oedema—and is often mistaken for cellulitis.

16.18 Chronic peripheral oedema and lymphoedema 3819 feet. This gives rise to a disproportionate, large, pear-shaped lower half with thick, heavy, chunky legs (Fig. 16.18.7). The skin is soft, tender, and bruises easily. Pain may be a striking feature. Distinction from a gynoid-distributed obesity or a ‘fatty’ lymphoedema may be difficult, but lipoedema is not influenced by dieting and is there- fore distinct from morbid obesity. Lipoedema is probably a genetic condition with either X-linked dominant inheritance or, more likely, autosomal dominant inheritance with sex

limitation. Clinical investigation The investigation of choice for confirming that oedema is primarily of lymphatic origin is lymphoscintigraphy (isotope lymphography). Traditional direct-contrast radiographic lymphography is now rarely undertaken to investigate lymphoedema. MRI or CT is of value in identifying a cause for lymphatic obstruction (e.g. cancer). Indocyanine Green lymphography has recently been developed to facilitate imaging of superficial lymphatic collecting vessels. Lymphoscintigraphy A radiolabelled protein or colloid is administered via a subcuta- neous or intradermal injection, and its absorption and transport through lymphatic vessels to lymph nodes is imaged by gamma camera. Theoretically, lymphoscintigraphy permits examination of lymph drainage from any site to which radiolabelled tracer can be administered, as has happened with sentinel node mapping for melanoma, breast, and genital cancer management. For the investigation of a swollen limb, tracer is administered bilaterally into feet or hands. Lymph drainage routes can be crudely imaged and abnormalities identified (Fig. 16.18.8). Offline calculation of time–activity curves over regions of interest permit quantitative analysis of lymph drainage. Lymphoscintigraphy is very specific (i.e. there are few false positives), but it can be normal in the pres- ence of lymphoedema. Quantification (i.e. calculation of lymph transport) is important as imaging alone can miss lymphoedema where anatomy is normal but function is reduced. Indocyanine green lymphography Indocyanine green lymphography involves the intradermal injec- tion of indocyanine green, which is taken up by local lymphatics and transported to the sentinel lymph node. The use of a near infrared camera images the lymphatic vessels, as well as their active contrac- tions, and indicates the direction of lymph drainage. The technique is used for sentinel lymph node mapping prior to node biopsy in cancer management, particularly breast cancer and melanoma. It is also used in supermicrosurgery to identify subcutaneous lymph ves- sels suitable for anastomosis with small veins, so-called lymphatico- venular anastomosis, as treatment for lymphoedema. MRI MRI (or CT) demonstrates a thicker skin and a ‘honeycomb’ pat- tern in the swollen subcutaneous compartment of lymphoedema. Following deep vein thrombosis of the leg the subfascial muscle Fig. 16.18.7 Lipoedema—a condition almost exclusive to women resulting in excess subcutaneous fat on hips, buttocks, thighs, or legs giving rise to disproportionately large lower limbs and often mistaken for lymphoedema. Fig. 16.18.8 Lymphoscintigraphy is the investigation of choice for determining if limb swelling is due to lymphoedema. Following a web space injection (hand or foot) of a radiolabelled colloid (99mTc–antimony sulphide colloid) the transport of radioactivity
is imaged by gamma camera. Image abnormalities or a quantitative reduction in radioactivity in a region of interest within draining lymph nodes indicates lymphoedema. (a) Normal lymphoscintigraphy. (b) A patient with Milroy’s disease and identified mutation in the VEGFR3 gene giving rise to dysfunctional initial (absorbing) lymphatics
in the feet. (c) A patient with lymphoedema–distichiasis due to mutation in the FOXC2 gene that results in lymph reflux due to lymphatic valve failure.

section 16 Cardiovascular disorders 3820 compartment is enlarged, but not so in lymphoedema. MRI and CT are more objective than ultrasonography for identifying enlarged lymph nodes or pathology responsible for lymphatic obstruction such as pelvic tumour. MRI can be helpful to differentiate fat from fluid in cases of lipoedema/lipodystrophy and where there is tissue overgrowth of fat or muscle (e.g. Proteus syndrome). MR Lymphangiography utilizes a contrast agent that enters the lymphatic vessels to highlight them and the lymph nodes. Long examination times and discrimination of lymph vessels from veins limit this type of investigation. Colour Doppler duplex ultrasound Venous disease (primary varicose veins or post-thrombotic syn- drome) may

cause or contribute to lower limb swelling. Venous du- plex ultrasonography is helpful for identifying venous reflux. Iliac vein thrombosis or compression can be a cause of whole-leg swelling. Gene testing Gene testing is now the definitive means of diagnosing several lymphoedema genotypes, one example being Milroy disease (mu- tations in VEGFR3). With at least 12 causal genes now known for primary lymphoedema the use of a gene panel for clinical testing is becoming more commonplace. Treatment Physical therapy to stimulate lymph drainage No drug therapy is known to improve lymph drainage. The treat- ment of lymphoedema relies on improving lymph drainage through the application of simple physiological principles known to stimu- late lymph flow, while at the same time restoring any excessive ca- pillary filtration to as near normal as possible. The principles of treatment are generic, but obviously vary according to individual circumstances dependent on site (e.g. facial vs. leg lymphoedema), and cause (e.g. genetic lymphoedema in a child vs. lymphoedema in advanced cancer). Unlike blood flow, which is predominantly driven by the heart, lymph flow falls to low levels unless stimulated by movement and in particular exercise. Alternating changes in interstitial fluid pressure (by active or passive exercise or massage) increase ini- tial lymphatic filling and flow within initial lymphatics. Increases in lymph load (from higher microvascular fluid filtration) to col- lecting lymphatics will stimulate greater contractility within these main pumping vessels. Patients with leg lymphoedema often notice that walking re- duces swelling. The addition of a bandage or stocking will enhance the effect of movement. The idea of compression is not to squeeze fluid out of the limb with force, like squeezing toothpaste out of a tube, but to create an outer envelope to the leg that resists expan- sion of the calf muscle during contraction. This generates a high interstitial pressure during muscle contractions to drive lymph drainage. Low pressures during skeletal muscle relaxation permit lymphatic vessel refilling before further muscle contraction repeats the cycle. Compression without movement (active or passive exer- cises) does not improve lymph drainage. Isotonic muscle exercise and compression is particularly helpful in circumstances where lymphatic collector contractility is impaired (normally once lymph has entered a lymphatic collecting vessel, smooth muscle contrac- tions drive lymph forwards and valves ensure unidirectional flow). Compression has the added benefit of lowering venous pressure in the leg, so reducing microvascular fluid filtration and therefore lymph load. Manual lymphatic drainage therapy, a specific form of lymphatic massage, operates on the same principle of stimulating alternating rises and falls in interstitial pressure and is used to decongest more proximal regions of the body (e.g. the adjoining quadrant of the trunk to a swollen limb, through which lymph from the limb needs to pass before being directed to a normally functioning lymphatic basin). In right-arm lymphoedema, manual lymphatic drainage would serve to direct collateral lymph drainage to normally draining lymph routes in the contralateral left axilla and so complement the effect of any compression and exercise to the right arm. In moderate to severe lymphoedema, treatment with an inten- sive course of manual lymphatic drainage, multilayer lymphoedema bandaging, and exercise (decongestive lymphatic therapy/combined decongestive therapy) can reverse more or less all the comorbidity from swelling, including ‘elephantiasis’ skin changes. Once swelling has been reduced and limb shape improved, control is maintained through exercise while wearing appropriately fitted compres- sion garments. In elderly and infirm individuals, the application and removal of hosiery can be problematic, but most patients will manage if good technique is taught and aids to application provided. Compression wraps with Velcro attachments (e.g. Farrow wraps) provide easily applied graduated support. Elevation of the legs is often wrongly chosen over exercise as treat- ment for lymphoedema. Elevation helps oedema by lowering venous pressure and consequently reducing capillary pressure. This reduces lymph load but does not improve lymph

drainage. Nevertheless, it allows base line levels of lymph drainage to ‘catch up’ with demand. While exercise is preferred to elevation as treatment, elevation is re- commended during periods of rest. Intermittent pneumatic compression pumps probably displace fluid as much as improve lymph flow. Nevertheless, they can simu- late the massaging effects of movement and reduce high venous pres- sures, and thereby prove helpful for patients spending considerable time in chairs, or those with venous hypertension for other reasons. Prevention of infection The main risk factors for cellulitis (erysipelas) or Acute Dermato- Lymphangio-Adenitis are lymphatic insufficiency and loss of skin integrity (wounds, interdigital skin breaks, and leg ul- cers). Good skin care is the first consideration when treating lymphoedema. This has been well demonstrated in elephantiasis and podoconiosis. Avoidance of skin damage (including sterile needle puncture), good hygiene, regular emollients, treatment of any dermatitis or fungal infection, and antisepsis following minor wounds are im- portant. Consensus recommendations for the treatment of cellulitis with lymphoedema are found in Table 16.18.2 and at http://www. thebls.com/cellulitis. Recurrent cellulitis can be a particular problem. Prophylactic phenoxymethylpenicillin 250 mg twice daily for 12 months halves rates of infection compared to placebo. Obesity, multiple previous

 attacks, and lymphoedema are associated with increased failure of prophylaxis. Drug therapy Too often diuretics are prescribed for oedema on an empirical basis, without due thought for the underlying pathophysiology. They have very little effect in established lymphoedema because their main action is in the kidneys to excrete body salt and water, and so in turn reduce microvascular fluid filtration and lymph load. They should really only be prescribed in circumstances of salt and water retention, whereupon spironolactone may be pre- ferred. Rutoside (a glycoside) and flavonoids have been advocated, but clinical effect is minimal. Calcium channel antagonists should be avoided in lymphoedema because they encourage oedema. The mechanism is unclear, but lymphatic pumping is paralysed by this class of drug in animal studies. Surgery Surgery can involve removal of excess tissue (reducing/debulking operations or liposuction) or bypassing of local lymphatic defects, but traditional debulking or reducing surgical operations are now rarely performed. Because excess fat can make up a considerable component of the swelling, suction lipectomy (liposuction) is now an accepted treatment for severe lymphoedema or lymphoedema where fat is the dominant tissue component. However, surgery can be effective in selected patients. Supermicrosugical lymphatico-venular anastomoses join obstructed lymphatics to small veins to enhance lymph drainage and can succeed in reducing swelling and frequency of cellulitis. Vascularized lymph node transfer seeks to transplant an autologous lymph node from one normally draining lymph node basin to a compromised basin in order to reconstitute lymph drainage through stimulating lymphangiogenesis in the re- cipient site. Surgery often does not obviate the need for long-term compression garments. Lymphoedema in other sites Genital Genital lymphoedema may arise from a genetic fault in lymph- atic development, in which case internal lymph problems (e.g. intestinal lymphangiectasia), and leg lymphoedema may coexist. Acquired forms may result from filariasis, cancer treatment, in- fection (cellulitis), anogenital granulomatosis/Crohn’s disease, and hidradenitis suppurativa. Control of any inflammation is essential for control of oedema. Facial Impaired lymph drainage within skin and subcutaneous local lymphatics is likely to be a factor in cases of facial swelling, par- ticularly periorbital oedema associated with rosacea, dermato-myositis, and thyroid disease. Head and neck lymphoedema has become a greater burden with the increased incidence of head and neck cancer treatment. FURTHER READING Aspelund A, et al. (2016). Lymphatic system in cardiovascular medicine. Circ Res, 118, 515–30. British Lymphology

Society (2005). Consensus document on the management of cellulitis in lymphoedema. http://www.thebls.com/ concensus. php Table 16.18.2 Antibacterials for cellulitisa,b Situation First-line antibacterials If allergic to penicillin Second-line antibacterials Comments Acute cellulitis

- septicaemia (inpatient admission) Flucloxacillin 1–2 g IV q6 hc,6 or amoxicillin 2 g IV q8 hc (see main text) Clindamycin
  600 mg IV q6 h13 Clindamycin 600 mg IV q6 h (if poor or no response by 48 h) Switch to PO flucloxacillin 500 mg q.d.s. or amoxicillin 500 mg t.d.s. or clindamycin 300 mg q.d.s. when: no fever for 48 h and inflammation much resolved and falling CRP. Then continue as below. Acute cellulitis (home care) or emergency back-up supply of antibacterials Flucloxacillin 500 mg q.d.s. or amoxicillin 500 mg t.d.s.d Erythromycine 500 mg q.d.s. or clarithromycine 500 mg b.d. Clindamycin 300 mg q.d.s. If fails to resolve, convert to first-line IV regimen above Give for a minimum of 2 weeks. Continue antibacterials until the acute inflammation has completely resolved; in severe cases this may take 1–2 months. (Note: residual ‘staining’ may persist beyond this.) Prophylaxis if 2+ episodes of cellulitis per year Phenoxymethylpenicillin
  250 mg b.d. (500 mg b.d.
  if BMI ≥33)14 Erythromycine
  250 mg once daily or clarithromycine 250 mg once daily Clindamycin 150 mg once daily or doxycycline 50 mg once dailyf Continue for 2 years, after 1 year, halve the dose of phenoxymethylpenicillin; if acute cellulitis develops after dose reduction/discontinuation, treat the acute cellulitis, and then commence life-long prophylaxis a but follow local guidelines, particularly for IV antibacterials b PO unless stated otherwise c add gentamicin 5 mg/kg IV daily for 1 week if anogenital region involved, adjust dose according to renal function and gentamicin plasma concentration d if Staph. aureus infection suspected (folliculitis, pus formation, crusted dermatitis), flucloxacillin 500 mg q.d.s. should definitely be used e for patients taking astemizole, tolterodine, or statins, do not prescribe macrolide antibacterials (clarithromycin, erythromycin) f in these circumstances, review by local specialist lymphoedema services and advice from a microbiologist is recommended. There is a need to balance the use of certain antibiotics (e.g. clindamycin, cefalexin) as prophylaxis against the risk of predisposing to C. difficile infection.

section 16 Cardiovascular disorders 3822 Brorson H (2016). Liposuction in lymphedema treatment. J Reconstr Microsurg, 32, 56–65. Browse NL, Burnand KG, Mortimer PS (2003). Diseases of the lymphatics. Arnold, London. Burnier P, et al. (2017). Indocyanine green applications in plastic surgery: a review of the literature. J Plast Reconstr Aesthet Surg, 70, 814–27. Carl HM, et al. (2017). Systematic review of the surgical treatment of extremity lymphedema. J Reconstr Microsurg, 33, 412–25. Child AH, et al. (2010). Lipedema: an inherited condition. Am J Med Genet A, 152A, 970–6. Connell FC, et al. (2013). The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. Clin Genet, 84, 3031–4. DiSipio T, et al. (2013). Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol, 14, 5001–5. Foldi M, Foldi E, Kubik S (2003). Textbook of lymphology for physicians and lymphoedema therapists. Urban & Fischer, San Francisco, CA. International Society of Lymphology (2013). The diagnosis and treat- ment of peripheral lymphedema: 2013 consensus document of the International Society of Lymphology. Lymphology, 46, 1–11. Keppler-Noreuil KM, et al. (2015). PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, dif- ferential diagnosis, and evaluation. Am J Med

Genet A, 167A, 287–95. Keramida G, et al. (2017). Importance of accurate ilio-inguinal quantification in lower extremity lymphoscintigraphy. Nucl Med Commun, 38, 209–14. Lee BB, et al. (2013) Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2013. Int Angiol, 32, 541–74. Levick JR (2009). An introduction to cardiovascular physiology, 5th edi- tion. CRC Press, London. Levick JR, Michel CC (2010). Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res, 87, 1982–10. Lymphoedema Framework Project (2006). Best practice for the manage- ment of lymphoedema, international consensus. Medical Education Partnership, London. http://www.lympho.org/mod_turbolead/up- load/file/Lympho/Best_practice_20_July.pdf Moffatt C, et al. (2003). Lymphoedema: an underestimated health problem. Q J Med, 96, 731–8. Moffatt CJ, et al. (2017). Chronic oedema: a prevalent health care problem for UK health services. Int Wound J, 14, 772–81. Mortimer PS, Levick JR (2004). Chronic peripheral oedema: the crit- ical role of the lymphatic system. Clin Med, 4, 4448–53. NICE Interventional procedures guidance; liposuction for chronic lymphoedema. Nutman TB (ed) (2000). Lymphatic filariasis. Imperial College Press, London. Tekola Ayele F, et al. (2012). HLA class II locus and susceptibility to podoconiosis. N Engl J Med, 366, 1200–8. Thomas KS, et al.; UK Dermatology Clinical Trials Network’s PATCH I Trial Team (2013). Penicillin to prevent recurrent leg cellulitis. N Engl J Med, 368, 1695–703. Twycross RG, Wilcock A, Howard P (2014). Palliative care formulary, 5th edition. http://www.palliativedrugs.com Zuther JE, Norton S (2013). Lymphedema management, 3rd edition. Thieme, New York.

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