TABLE 50-2 DRUGS ASSOCIATED WITH EDEMA FORMATION

Nonsteroidal anti-inflammatory drugs
Antihypertensive agents
Direct arterial/arteriolar vasodilators
Hydralazine
Clonidine
Methyldopa
Guanethidine
Minoxidil
Calcium channel antagonists
α-Adrenergic antagonists
Thiazolidinediones
Steroid hormones
Glucocorticoids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
Interleukin 2
OKT3 monoclonal antibody

Source: Modified from Chertow GM: Approach to the patient with edema, in *Primary Cardiology*, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

when famished subjects are first provided with an adequate diet. The ingestion of more food may increase the quantity of sodium ingested, which is then retained along with water. So-called refeeding edema also may be linked to increased release of insulin, which directly increases tubular sodium reabsorption. In addition to hypoalbuminemia, hypokalemia and caloric deficits may be involved in the edema of starvation.

LOCALIZED EDEMA

In this condition, the hydrostatic pressure in the capillary bed upstream (proximal) of the obstruction increases so that an abnormal quantity of fluid is transferred from the vascular to the interstitial space. Since the alternative route (i.e., the lymphatic channels) also may be obstructed or maximally filled, an increased volume of interstitial fluid in the limb develops (i.e., there is trapping of fluid in the interstitium of the extremity). The displacement of large quantities of fluid into a limb may occur at the expense of the blood volume in the remainder of the body, thereby reducing effective arterial blood volume and leading to the retention of NaCl and H_2O until the deficit in plasma volume has been corrected.

Localized edema due to venous or lymphatic obstruction may be caused by thrombophlebitis, chronic lymphangitis, resection of regional lymph nodes, and filariasis, among other causes. Lymphedema is particularly intractable because restriction of lymphatic flow results in increased protein concentration in the interstitial fluid, a circumstance that aggravates fluid retention.

Other Causes of Edema These causes include hypothyroidism (myxedema) and hyperthyroidism (pretibial myxedema secondary to Graves' disease), the edema in which is typically nonpitting and due to deposition of hyaluronic acid and, in Graves' disease, lymphocytic infiltration and inflammation; exogenous hyperadrenocortism; pregnancy; and administration of estrogens and vasodilators, particularly dihydropyridines such as nifedipine.

DISTRIBUTION OF EDEMA

The distribution of edema is an important guide to its cause. Edema associated with heart failure tends to be more extensive in the legs and to be accentuated in the evening, a feature also determined largely by posture. When patients with heart failure are confined to bed, edema may be most prominent in the presacral region. Severe heart failure may cause ascites that may be distinguished from the ascites caused by hepatic cirrhosis by the jugular venous pressure, which is usually elevated in heart failure and normal in cirrhosis.

Edema resulting from hypoproteinemia, as occurs in the nephrotic syndrome, characteristically is generalized, but it is especially evident in the very soft tissues of the eyelids and face and tends to be most pronounced in the morning owing to the recumbent posture assumed during the night. Less common causes of facial edema include trichinosis, allergic reactions, and myxedema. Edema limited to one leg or to one or both arms is usually the result of venous and/or lymphatic obstruction. Unilateral paralysis reduces lymphatic and venous drainage on the affected side and may also be responsible for unilateral edema. In patients with obstruction of the superior vena cava, edema is confined to the face, neck, and upper extremities in which the venous pressure is elevated compared with that in the lower extremities.

APPROACH TO THE PATIENT: Edema

An important first question is whether the edema is localized or generalized. If it is localized, the local phenomena that may be responsible should be considered. If the edema is generalized, one should first determine if there is serious hypoalbuminemia, e.g., serum albumin <25 g/L. If so, the history, physical examination, urinalysis, and other laboratory data will help evaluate the question of cirrhosis, severe malnutrition, or the nephrotic syndrome as the underlying disorder. If hypoalbuminemia is not present, it should be determined if there is evidence of heart failure severe enough to promote generalized edema. Finally, it should be ascertained as to whether or not the patient has an adequate urine output or if there is significant oliguria or anuria. **These abnormalities are discussed in Chaps. 61, 334, and 335.**

51e Approach to the Patient with a Heart Murmur

Patrick T. O'Gara, Joseph Loscalzo

This is a digital-only chapter. It is available on the DVD that accompanies this book, as well as on Access Medicine/Harrison's Online, and the eBook and "app" editions of HPIM 19e.

The differential diagnosis of a heart murmur begins with a careful assessment of its major attributes and response to bedside maneuvers. The history, clinical context, and associated physical examination findings provide additional clues by which the significance of a heart murmur can be established. Accurate bedside identification of a heart murmur can inform decisions regarding the indications for noninvasive testing and the need for referral to a cardiovascular specialist. Preliminary discussions can be held with the patient regarding antibiotic or rheumatic fever prophylaxis, the need to restrict various forms of physical activity, and the potential role for family screening.