Diffetential diagnosis of edemas, ascites and fluidothorax

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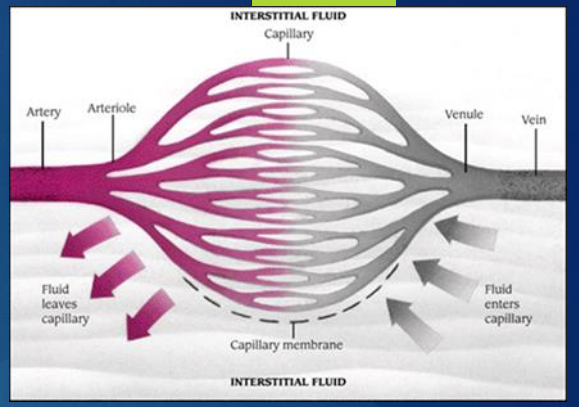
Edema

- a palpable swelling produced by expansion of the interstitial fluid volume
- Anasarca - massive and generalized excess of the interstitial fluid

Pathophysiology of edema

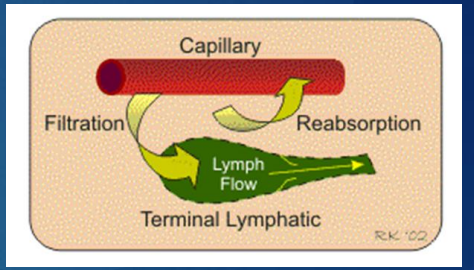
- 1/3 of the total body water is in the extracellular space
- 2/3 in the intracellular
- Extracellular fluid = intravascular plasma volume (25%) + interstitial fluid (75%)
- Generalized edema is seen when the interstitial volume increases by 2.5-3 liters

Pathophysiology of edema



There are two basic steps involved in edema formation:

- An alteration in capillary hemodynamics that favors the movement of fluid from the vascular space into the interstitium
- The retention of dietary or intravenously administered sodium and water by the kidneys



- Edema (other than localized edema as with an allergic reaction) does not become clinically apparent until the interstitial volume has increased by at least 2.5 to 3 liters. Since the normal plasma volume is only approximately 3 liters, it is clear that patients would develop marked hemoconcentration and shock if the edema fluid were derived only from the plasma

Pathophysiology of edema

Systemic causes:

- increase in capillary hydrostatic pressure
- decrease in oncotic pressure of blood plasma
- increase in oncotic interstitial pressure
- capillary permeability disorder

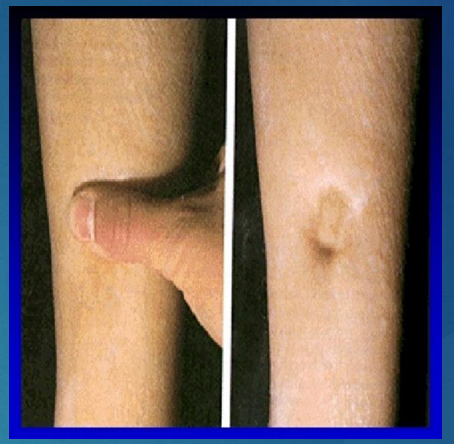
Major causes of edema by primary mechanism

Increased capillary hydraulic pressure
Increased plasma volume due to renal sodium retention
Heart failure, including cor pulmonale
Primary renal sodium retention
▪ Renal disease, including the nephrotic syndrome
▪ Drugs:* Nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, fludrocortisone, thiazolidinediones (glitazones), insulins, estrogens, progestins, androgens, testosterone, aromatase inhibitors, tamoxifen; and by multiple mechanisms: vasodilators (hydralazine, minoxidil, diazoxide) and calcium channel blockers (particularly dihydropyridines [ie, amlodipine, nifedipine]); also refer to "Arteriolar vasodilation" below
▪ Refeeding edema
▪ Early hepatic cirrhosis
Pregnancy and premenstrual edema
Idiopathic edema, when diuretic induced
Sodium or fluid overload: Parenteral antibiotics or other drugs with large amounts of sodium, sodium bicarbonate, or excessive or overly rapid fluid replacement
Venous obstruction or insufficiency
Cirrhosis or hepatic venous obstruction
Acute pulmonary edema
Local venous obstruction
▪ Venous thrombosis
▪ Venous stenosis
Chronic venous insufficiency – Post-thrombotic syndrome
Arteriolar vasodilation
Drugs:* Frequent – Vasodilators (hydralazine, minoxidil, diazoxide), dihydropyridine calcium channel blockers; less frequent – alpha1 blockers, sympatholytics (ie, methyldopa), nondihydropyridine calcium channel blockers[1]
Idiopathic edema (?)
Hypoalbuminemia
Protein loss
Nephrotic syndrome
Protein-losing enteropathy
Reduced albumin synthesis
Liver disease
Malnutrition
Increased capillary permeability
Idiopathic edema
Burns
Trauma
Inflammation or sepsis
Allergic reactions, including certain forms of angioedema
Acute respiratory distress syndrome
Diabetes mellitus
Interleukin 2 therapy
Malignant ascites
Lymphatic obstruction or increased interstitial oncotic pressure
Lymph node dissection
Nodal enlargement due to malignancy
Hypothyroidism
Malignant ascites
Other drugs* (uncertain mechanism)
Anticonvulsant: Gabapentin, pregabalin
Antineoplastic: Docetaxel, cisplatin
Antiparkinson: Pramipexole, ropinirole

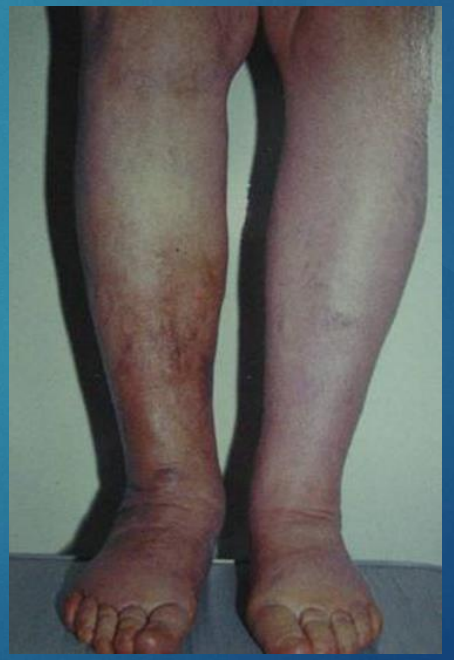
* Patients with decreased cardiac output, preexisting renal insufficiency, and/or receiving higher doses are more likely to experience edema and edema-associated adverse events. This is not a complete list of drugs associated with edema. For additional information, refer to the Lexicomp individual drug monographs included with UpToDate.

Reference:

1. *Messerli FH. Vasodilatory edema: A common side effect of antihypertensive therapy. Curr Cardiol Rep 2002; 4(6):479.*



pitting edema



non-pitting edema

Etiology of edema

The most common causes of generalized edema:

- Heart failure
- Cirrhosis
- Nephrotic syndrome and other forms of kidney disease
- Premenstrual edema and pregnancy

Pathophysiology of edema - cardiac

- increased venous hydrostatic pressure (cor pulmonale, constriction pericarditis, tricuspid valve defect)
- decrease in cardiac output → decrease in effective circulating blood volume and arterial filling → activation of the renin-angiotensin-aldosterone system → ADH flushing + increase in sympathetic activity in the kidneys → water and Na retention → extracellular fluid volume increases

Pathophysiology of edema - nefrogenic

- sodium and water retention
- nephrotic syndrome - proteinuria 3.5 g/d
- oligo/anuria
- inflammatory diseases with increased capillary permeability

Pathophysiology of edema - hepatic

- increased NO production → peripheral vasodilation
- reduction of the effective volume of circulating blood → reduced filling of the arterial system → activation of the renin-angiotensin-aldosterone system → flushing of ADH + increase of sympathetic activity in the kidneys → retention of water and Na → volume of extracellular fluid increases
- hypalbuminemia

Pathophysiology of edema - hypoalbuminemia

- reduction of oncotic pressure → transfer of water to the interstitium
- reduction of the effective volume of circulating blood → reduced filling of the arterial system → activation of the renin-angiotensin-aldosterone system → leaching of ADH + increase of sympathetic activity in the kidneys → retention of water and Na → volume of extracellular fluid increases

Pathophysiology of edema - hypoalbuminemia

- reduction of oncotic pressure → transfer of water to the interstitium
- reduction of the effective volume of circulating blood → reduced filling of the arterial system → activation of the renin-angiotensin-aldosterone system → leaching of ADH + increase of sympathetic activity in the kidneys → retention of water and Na → volume of extracellular fluid increases

Pathophysiology of edema – allergic and angioedema

- IgE antibody-mediated allergies - mast cell binding - histamine release - increased capillary permeability
- Angioedema
- Hereditary or acquired C1 protein inhibitor defect

Clinical manifestation and evaluation of edema

- **Peripheral edema:** pitting or nonpitting

  - pitting edema - presence of tissue depression after pressure at least 5 sec and reflects movement of the excess interstitial water in response to pressure

  grading from 1+ to 4+ (mild to severe)

  - nonpitting edema suggests lymphatic obstruction, hypothyroidism

  - locates preferentially in the dependent areas (lower extremities, sacrum)

Clinical manifestation and evaluation of edema

- **Peripheral edema:** pitting or nonpitting
  - Leg edema: unilateral/asymmetric edema or bilateral edema, acuity of edema
    - Acute onset of unilateral leg edema raises concern for deep vein thrombosis
    - Bilateral edema (frequent in older adults) - usually chronic rather than acute -- chronic venous disease, heart failure, venodilating medications, or pulmonary hypertension (the most commonly missed cause of bilateral edema)

Major causes of bilateral lower extremity edema

Acute edema

- Medications
- Heart failure
- Nephrotic syndrome
- Venous thrombosis
- Acute worsening of chronic causes

Chronic edema

- Venous insufficiency
- Heart failure
  - Left-sided with preserved or reduced ejection fraction
  - Right-sided
    - Pulmonary hypertension (including sleep apnea)
  - Restrictive pericarditis
  - Restrictive cardiomyopathy
- Renal disease (including nephrotic syndrome)
- Liver disease (early cirrhosis)
- Premenstrual edema
- Pregnancy
- Malnutrition (including malabsorption and protein losing enteropathy)
- Pelvic compression (including tumor or lymphoma)
- Dependent edema
- Sodium or fluid overload (including parenteral fluids, antibiotics and other drugs with large amounts of sodium)
- Refeeding edema
- Idiopathic edema
- Inflammation (including sepsis)
- Medications

Chronic lymphedema

- Primary lymphedema (presenting in childhood)
- Secondary lymphedema (including lymph node dissection)
- Thyroid disease (myxedema)

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Clinical manifestation and evaluation of edema

- **approach to patients with acute unilateral or asymmetric leg edema:**
  - clinical probability of DVT and perform appropriate diagnostic testing depending upon the clinical probability (Wells score and modified Wells score)
  - if DVT excluded, then rule out other causes: muscle strain, tear, or twisting injury to the leg (40%), leg swelling in a paralyzed limb (9%), lymphangitis or lymph obstruction (7%), venous insufficiency (7%), popliteal (Baker's) cyst (5%), cellulitis (3%), knee abnormality (2%), unknown (26%)

Clinical manifestation and evaluation of edema

- **Chronic unilateral or asymmetric edema:** lower extremity chronic venous disease

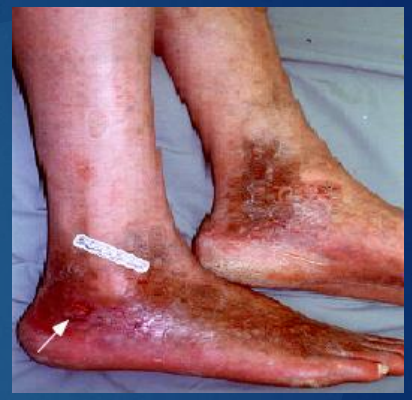
  - less common causes: primary or secondary lymphedema, pelvic neoplasm compromising venous return, and complex regional pain sy

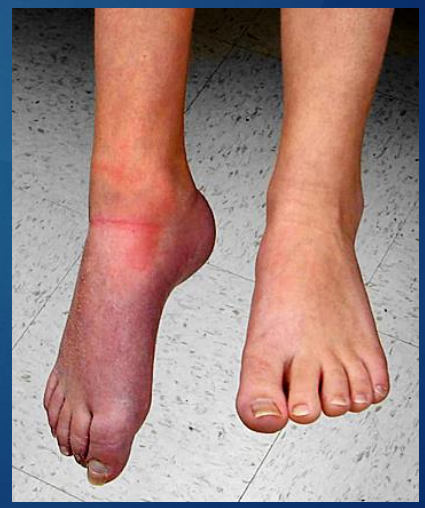
- **Approach to patients with chronic unilateral or asymmetric leg edema:**

  - chronic venous disease: history of thrombophlebitis in the affected leg (pigmentary changes and skin ulceration)

  - lymphedema: history of an ipsilateral inguinal or pelvic lymph node dissection, or of radiation therapy (initially pitting edema, but becomes non-pitting as cutaneous fibrosis occurs)

  - complex regional pain syndrome: occurs four to six weeks after limb trauma (pain, edema, and alteration in skin color and temperature)





Clinical manifestation and evaluation of edema

- **Acute bilateral leg edema:** uncommon

  most likely etiologies:

  1. side effect of medications, especially dihydropyridine calcium channel blockers
  2. acute heart failure
  3. acute nephrotic syndrome
  4. bilateral DVT, which is often associated with malignancy

Clinical manifestation and evaluation of edema

- **approach to patients presenting with acute bilateral leg edema:**

  - exclude DVT first

  - stop drugs known to cause edema

  - dyspnea, orthopnea, paroxysmal nocturnal dyspnea, tachypnea, tachycardia, rales, or distended neck veins - evaluated for acute heart failure

  - semi-quantitative urine dipstick

  - D-dimers

Clinical manifestation and evaluation of edema

- **Arm edema:** acuity of the edema

  - acute isolated upper extremity edema: trauma, infection, superficial thrombophlebitis, or inflammatory arthritis of the upper extremity

  - acute bilateral upper extremity edema (rare) may be seen with bilateral spontaneous venous thrombosis or superior vena cava syndrome

  - more gradual swelling of the arm occurs with lymphedema: primary (usually presenting in childhood) or secondary (usually following surgery or radiation treatment)

Clinical manifestation and evaluation of edema

- **Isolated pulmonary edema:** shortness of breath and orthopnea, tachypnea, rales, diastolic gallop (S3)
- common causes: cardiac disease (eg, acute myocardial infarction, heart failure, mitral or aortic valvular pathologies), volume overload due to primary renal sodium retention (such as acute glomerulonephritis) or by increased capillary permeability in the acute respiratory distress syndrome
- less common causes: forms of noncardiogenic pulmonary edema, including high-altitude pulmonary edema (HAPE), neurogenic pulmonary edema, and pulmonary edema related to opioid overdoseIn contrast to cardiac and renal disease, uncomplicated cirrhosis is **not** associated with pulmonary edema

Other forms of edema

- **Lymphedema:** most common in developed countries **-** axillary lymph node dissection in patients with breast cancer and axillary or inguinal lymph node dissection in patients with melanoma.

  - worldwide, the most common cause is filariasis (typically limited to an arm or leg; clinical hallmark is cutaneous and subcutaneous thickening, as manifested by cutaneous fibrosis, peau d'orange, and a positive Stemmer sign, which refers to an inability to tent the skin at the base of the digits

- **Nonpitting edema: due to 2 disorders:**

  1. moderate to severe lymphedema, as can occur after radical mastectomy or with lymphatic disease

  2. pretibial myxedema, which occurs in patients with thyroid disease and is associated with localized areas of swelling

- **Periorbital and scrotal edema:** localized forms of edema that can be seen in systemic edematous states but should **not** be the sole manifestation of edema in these disorders

Ascites

- accumulation of fluid within the peritoneal cavity

Causes of ascites

Cirrhosis	81 percent
Cancer	10 percent
Heart failure	3 percent
Tuberculosis	2 percent
Dialysis	1 percent
Pancreatic disease	1 percent
Other	2 percent

Data from: Runyon BA, Montano AA, Akriviadis EA, et al. Ann Intern Med 1992; 117:215.

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Rare causes of ascites

Infectious
Amebiasis
Ascariasis
Brucellosis
Chlamydia peritonitis
Complications related to HIV infection
Pelvic inflammatory disease
Pseudomembranous colitis
Salmonellosis
Whipple's disease
Hematologic
Amyloidosis
Castleman's syndrome
Extramedullary hematopoiesis
Hemophagocytic syndrome
Histiocytosis X
Leukemia
Lymphoma
Mastocytosis
Multiple myeloma
Miscellaneous
Abdominal pregnancy
Crohn's disease
Endometriosis
Gaucher's disease
Lymphangioleiomyomatosis
Myxedema
Nephrotic syndrome (in children, adults with nephrotic syndrome and ascites usually have another cause such as cirrhosis)
Operative lymphatic tear or ureteral injury
Ovarian hyperstimulation syndrome
POEMS syndrome
Systemic lupus erythematosus
Ventriculoperitoneal shunt

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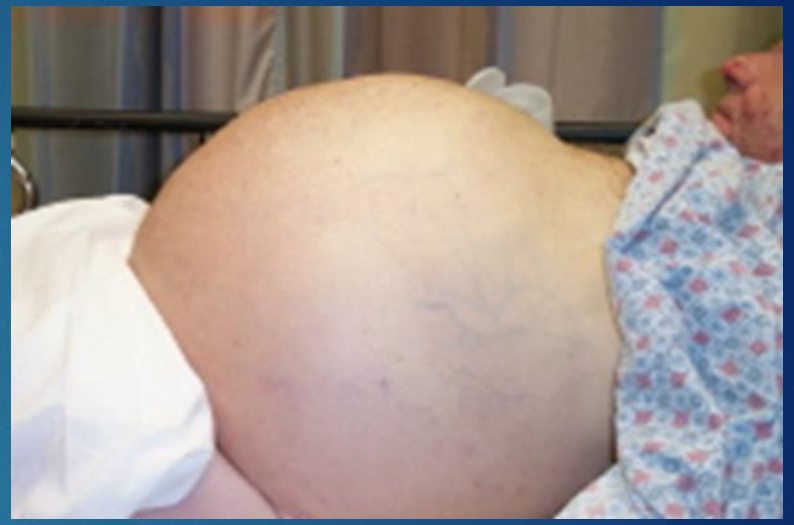
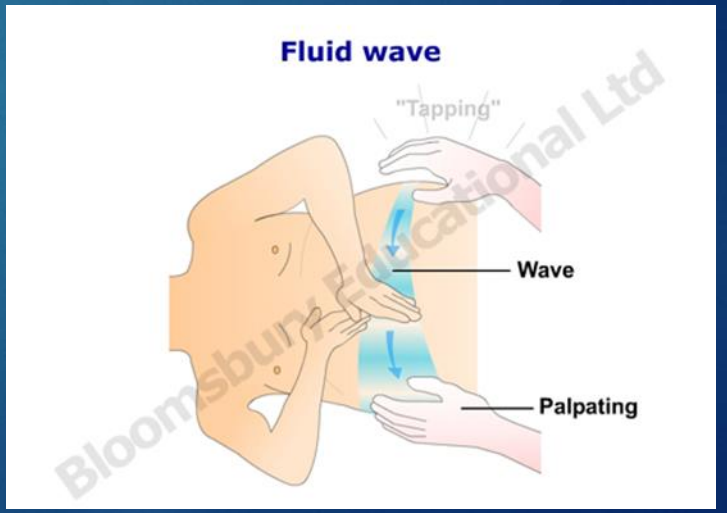




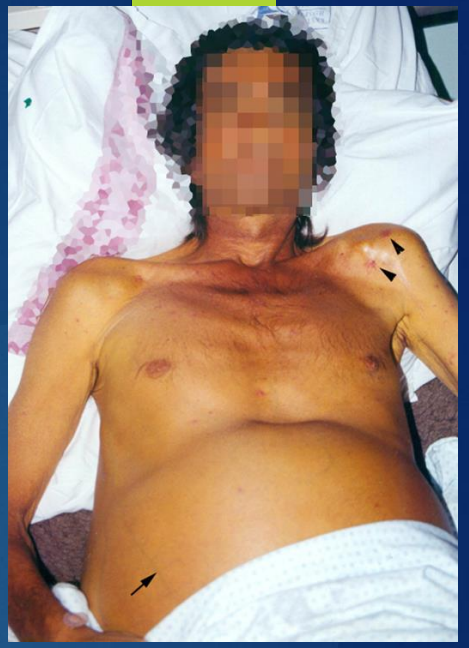
Pathophysiology of ascites

- **Portal hypertension**: cirrhosis, alcoholic hepatitis, acute liver failure, hepatic veno-occlusive disease (eg, Budd-Chiari syndrome), heart failure, constrictive pericarditis, hemodialysis-associated ascites (nephrogenic ascites)
- **Hypoalbuminemia**: nephrotic syndrome, protein-losing enteropathy, severe malnutrition
- **Peritoneal disease**: malignant ascites (eg, ovarian cancer, mesothelioma), infectious peritonitis (eg, TB or fungal infection), eosinophilic gastroenteritis, starch granulomatous peritonitis, peritoneal dialysis, multicystic mesothelioma (peritoneal inclusion cysts)
- **Other etiologies**: chylous ascites, pancreatic ascites (eg, from a disrupted pancreatic duct), myxedema, hemoperitoneum, urologic injury
- **Rare causes:** abdominal pregnancy, Whipple disease, and sarcoidosis
- 5% of patients have more than one cause (eg, cirrhosis + one of the following: tuberculosis peritonitis, peritoneal carcinomatosis, heart failure, or diabetic nephropathy

Pathophysiology of ascites in liver cirhosis

- Portal hypertension > 12 mmHg → opening of portocaval junctions → endotoxemia → increased activity of endothelial NO-synthase → vasodilation of splanchnic → reduction of the effective volume of circulating blood → reduced filling of the arterial bed → activation of the renin-angiotensin-aldosterone system → flushing of ADH + increase of sympathetic activity in the kidneys → retention of water and Na → volume of extracellular fluid increases
- hypalbuminemia

Clinical manifestation of ascites



- **Symptoms:** abdominal distension that may be painless or associated with abdominal discomfort

  - ascites due to cirrhosis and/or alcoholic hepatitis usually develops rapidly over a few weeks - weight gain, shortness of breath, early satiety, and dyspnea resulting from fluid accumulation and increased abdominal pressure

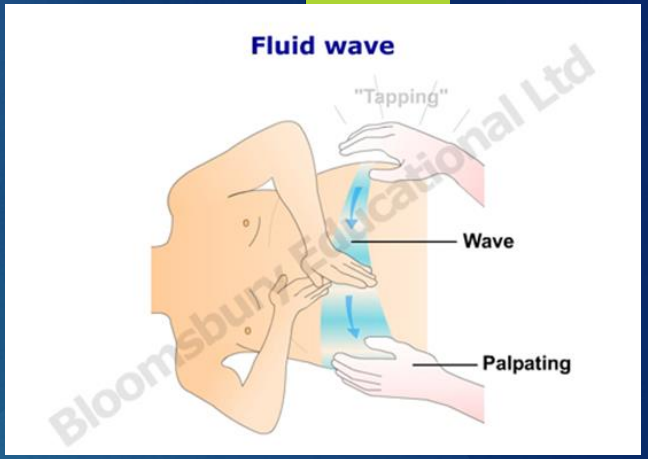
  - spontaneous bacterial peritonitis - fever, abdominal tenderness, and altered mental status

  - symptoms associated with hepatic decompensation, such as confusion or evidence of gastrointestinal bleeding.

  - malignant ascites - weight loss

  - ascites due to heart failure - dyspnea, orthopnea, and peripheral edema

Clinical manifestation of ascites



- **Physical examination:**

  - stigmata of cirrhosis (spider angioma, palmar erythema, abdominal wall collaterals)

  - jaundice, muscle wasting, gynecomastia, and leukonychia (white nails), palpable liver and spleen, parotid enlargement may be present but is probably due to alcohol and not cirrhosis per se

  - umbilical nodule – evidence for cancer as the cause of ascites (gastric cancer, colon cancer, hepatocellular carcinoma)

  - findings in heart failure: jugular venous distension, pulmonary congestion, or peripheral edema

Clinical manifestation of ascites

- **Laboratory tests**

  - cirrhosis or heart failure: abnormal liver and renal tests

  - cirrhosis: elevated INR, hypoalbuminemia, thrombocytopenia, anemia, leukopenia

  - spontaneous bacterial peritonitis: leukocytosis, metabolic acidosis, azotemia

Diagnosis of ascites

- physical examination, abdominal imaging (USG), paracentesis

Indications for abdominal paracentesis in a patient with ascites

New onset ascites
At the time of each admission to the hospital
Clinical deterioration, either inpatient or outpatient
Fever
Abdominal pain
Abdominal tenderness
Mental status change
Ileus
Hypotension
Laboratory abnormalities that may indicate infection
Peripheral leukocytosis
Acidosis
Worsening of renal function
Gastrointestinal bleeding (a high risk time for infection)

Reference: Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57:1651.

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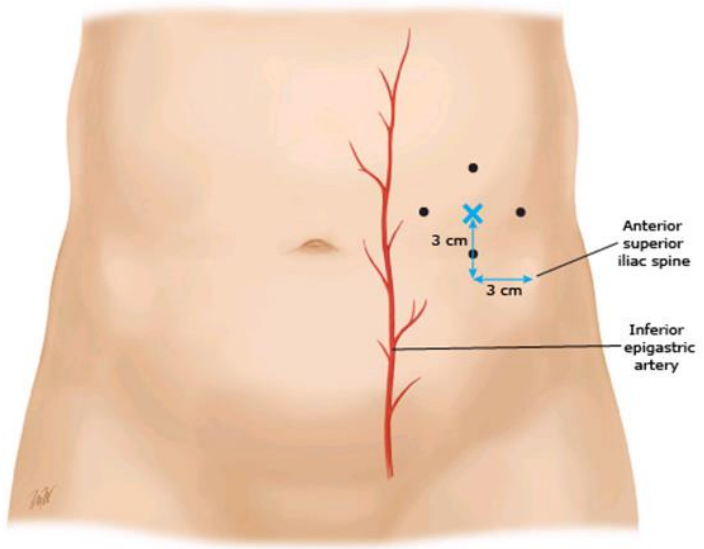
Abdominal paracentesis sites



Abdominal wall anatomy showing the author's preferred site for abdominal paracentesis and the inferior epigastric artery, which should be avoided.

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Diagnosis of ascites

- **General approach**

  Two of the main issues that arise regarding ascites are:

  - is the fluid infected?
  - is portal hypertension present?

  Initial tests that should be performed on the ascitic fluid include

  - appearance assessment (eg, clear, bloody, cloudy, milky)
  - serum-to-ascites albumin gradient determination (SAAG)
  - cell count and differential
  - total protein concentration

Diagnosis of ascites

Tests performed on ascitic fluid

Routine tests
Cell count and differential
Albumin concentration
Total protein concentration
Optional tests
Culture in blood culture bottles
Glucose concentration
Lactate dehydrogenase concentration
Gram stain
Amylase concentration
Unusual tests
Tuberculosis smear and culture
Adenosine deaminase activity
Cytology
Triglyceride concentration
Bilirubin concentration
Serum pro-brain natriuretic peptide
Carcinoembryonic antigen (CEA) concentration
Alkaline phosphatase concentration

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Classification of ascites by the serum-to-ascites albumin gradient

High albumin gradient (SAAG ≥1.1 g/dL)
Cirrhosis
Alcoholic hepatitis
Heart failure
Massive hepatic metastases
Heart failure/constrictive pericarditis
Budd-Chiari syndrome
Portal vein thrombosis
Idiopathic portal fibrosis
Low albumin gradient (SAAG <1.1 g/dL)
Peritoneal carcinomatosis
Peritoneal tuberculosis
Pancreatitis
Serositis
Nephrotic syndrome

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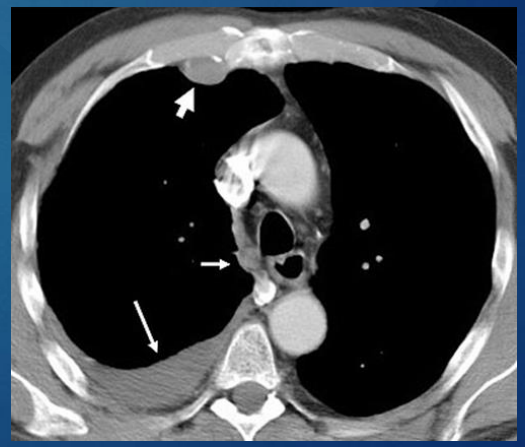
serum-to-ascites albumin gradient (SAAG) – identifies portal hypertension - more useful than the protein-based exudate/transudate concept

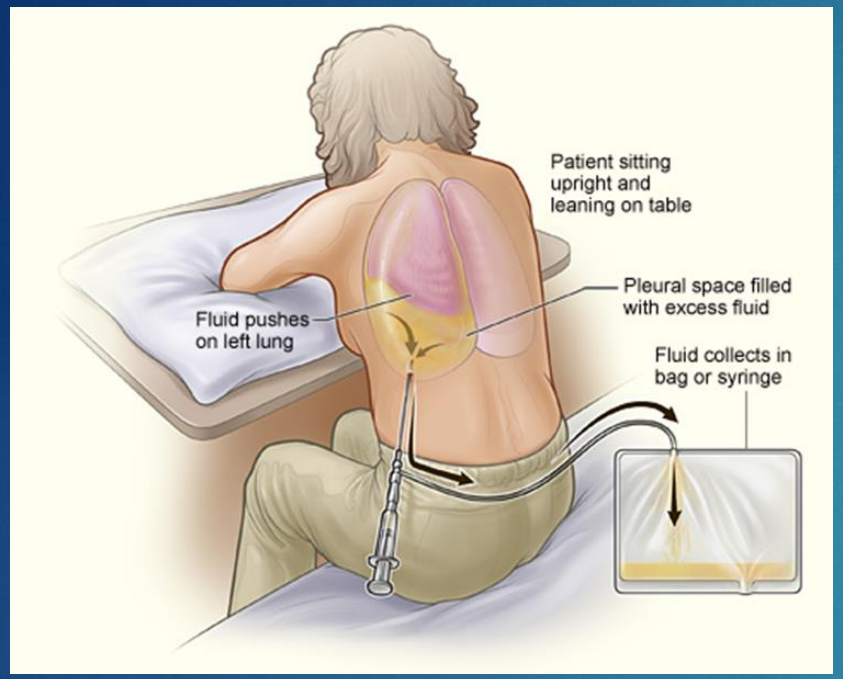
Pleural effusion

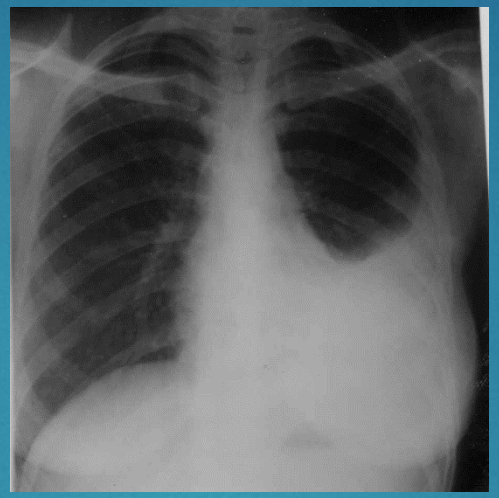
- Fluid in the pleural cavity - excessive production or insufficient resorption
- transsudate vs. exudate - according to the mechanism of origin and biochemistry

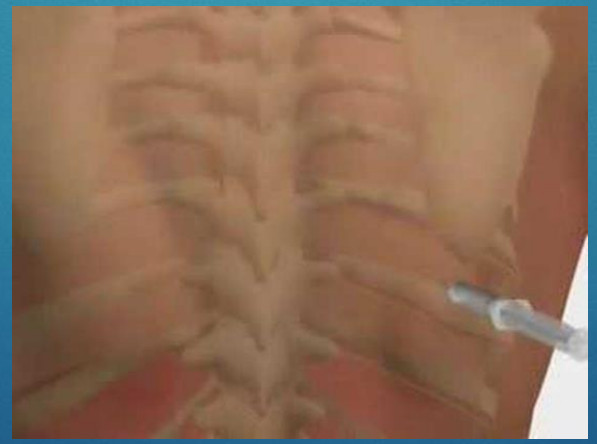
- Diagnosis:
  - history and physical examination
  - chest X-ray
  - chest CT
  - ultrasound



Conditions diagnosted by thoracocenthesis







Diagnoses established "definitively" by pleural fluid analysis

Disease	Diagnostic pleural fluid tests
Empyema	Observation (pus, putrid odor), positive culture
Malignancy	Positive cytology
Tuberculous pleurisy	Positive AFB stain, culture
Esophageal rupture	High salivary isoenzyme form of amylase, low pH (often as low as 6), ingested vegetable or meat fragments
Fungal-related effusions	Positive fungal stain, culture
Chylothorax	Triglycerides >110 mg/dL, chylomicrons by lipoprotein electrophoresis
Cholesterol effusion	Cholesterol >200 mg/dL with a cholesterol to triglyceride ratio >1, cholesterol crystals under polarizing light
Hemothorax	Ratio of pleural fluid to blood hematocrit >0.5
Urinothorax	Pleural fluid creatinine to serum ratio always >1 but diagnostic if >1.7
Peritoneal dialysis	Protein <0.5 mg/dL and pleural fluid to serum glucose ratio >1 in peritoneal dialysis patient
Extravascular migration or misplacement of a central venous catheter	Pleural fluid to serum glucose ratio >1, pleural fluid gross appearance mirrors infusate (eg, milky white if lipids infused)
Rheumatoid pleurisy	Cytologic evidence of elongated macrophages and distinctive multinucleated giant cells (tadpole cells) in a background of amorphous debris
Glycinothorax	Measurable glycine after bladder irrigation with glycine-containing solutions
Cerebrospinal fluid leakage into pleural space	Detection of beta-2 transferrin
Parasite-related effusions	Detection of parasites

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Pleural fluid analysis

- Gross appearance

Observations of pleural fluid helpful in diagnosis

	Suggested diagnosis
Color of fluid	
Pale yellow (straw)	Transudate, some exudates
Red (bloody)	Malignancy, benign asbestos pleural effusion, postcardiac injury syndrome, or pulmonary infarction in absence of trauma
White (milky)	Chylothorax or cholesterol effusion
Brown	Long-standing bloody effusion; rupture of amebic liver abscess
Black[1-4]	Aspergillus niger, Rhizomes oryzae, metastatic melanoma, pancreaticopleural fistula, crack cocaine use, bronchogenic adenocarcinoma, esophageal perforation during treatment with activated charcoal, chronic hemothorax
Yellow-green	Rheumatoid pleurisy
Dark green	Biliothorax
Color of:	
Enteral tube feeding	Feeding tube has entered pleural space
Central venous catheter infusate	Extravascular catheter migration
Character of fluid	
Pus	Empyema
Viscous	Mesothelioma
Debris	Rheumatoid pleurisy
Turbid	Inflammatory exudate or lipid effusion
Anchovy paste	Amebic liver abscess
Odor of fluid	
Putrid	Anaerobic empyema
Ammonia	Urinothorax

References:

1. *Chhabra A, Mukherjee V, Chowdhary M, et al. Black Pleural Effusion: A Unique Presentation of Metastatic Melanoma. Case Rep Oncol 2015; 8:222.*
2. *Huang TY, Tsai MJ. Education and imaging. Gastrointestinal: black pleural effusion induced by pancreaticopleural fistula. J Gastroenterol Hepatol 2013; 28:1798.*
3. *Jayakrishnan B, Dildar B, Rizavi DM, et al. Black pleural effusion. Lancet 2015; 386:e7.*
4. *Saraya T, Light RW, Takizawa H, Goto H. Black Pleural Effusion. Am J Med 2013; 126:641.e1.*

Pleural fluid analysis

Tests routinely performed on pleural fluid:

- cell count and cell differential
- pH
- protein
- lactate dehydrogenase (LDH)
- glucose

Pleural fluid analysis

- Light's traditional criteria: exsudate if at least one of the following criteria is presented:

  - pleural fluid protein/serum protein ratio greater than 0.5

  - pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6

  - pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH

Transudates are largely due to imbalances in hydrostatic and oncotic pressures in the chest

Causes of transudative pleural effusions

Causes of transudative effusions	Comment
Processes that *always* cause a transudative effusion	
Atelectasis	Caused by increased intrapleural negative pressure
Cerebrospinal fluid leak into pleural space	Thoracic spinal surgery or trauma and ventriculopleural shunts
Heart failure	Acute diuresis can result in borderline exudative features
Hepatic hydrothorax	Rare without clinical ascites
Hypoalbuminemia	Edema liquid rarely isolated to pleural space
Iatrogenic	Misplaced intravenous catheter into the pleural space; post Fontan procedure
Nephrotic syndrome	Usually subpulmonic and bilateral
Peritoneal dialysis	Acute massive effusion develops within 48 hours of initiating dialysis
Urinothorax	Caused by ipsilateral obstructive uropathy or by iatrogenic or traumatic GU injury
Processes that *may* cause a transudative effusion, but *usually* cause an exudative effusion	
Amyloidosis	Often exudative due to disruption of pleural surfaces
Chylothorax	Most are exudative effusions
Constrictive pericarditis	Bilateral effusions
Hypothyroid pleural effusion	From hypothyroid heart disease or hypothyroidism per se
Malignancy	Usually exudative, but 3 to 10 percent transudative possibly due to early lymphatic obstruction, obstructive atelectasis, or concomitant disease (eg, heart failure)
Pulmonary embolism	Most are exudative effusions
Sarcoidosis	Stage II and III disease
Superior vena caval obstruction	May be due to acute systemic venous hypertension or acute blockage of thoracic lymph flow
Nonexpandable lung*	A result of remote or chronic inflammation

GU: genitourinary.
* Trapped and entrapped lung are examples of nonexpandable lung. While trapped lung typically causes a transudative pleural effusion, entrapped lung is typically associated with an exudative effusion.

Exudates are caused by a variety of mechanisms, including infection, malignancy, immunologic responses, lymphatic abnormalities, noninfectious inflammation, and trauma

Causes of exudative pleural effusions

Infectious
Bacterial pneumonia
Tuberculous pleurisy
Parasites
Fungal disease
Atypical pneumonias (viral, mycoplasma)
Nocardia, Actinomyces
Subphrenic abscess
Hepatic abscess
Splenic abscess
Hepatitis
Spontaneous esophageal rupture
Cholecystitis
Iatrogenic or trauma
Central venous catheter misplacement/migration
Drug-induced (eg, nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, interleukin-2, procarbazine, methotrexate, clozapine, phenytoin, beta blocker, ergot drugs)
Esophageal perforation
Esophageal sclerotherapy
Enteral feeding tube in pleural space
Radiofrequency ablation of pulmonary neoplasms
Hemothorax
Chylothorax
Malignancy-related
Carcinoma
Lymphoma
Mesothelioma
Leukemia
Chylothorax
Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia)
Paramalignant effusions
Other inflammatory disorders
Pancreatitis (acute, chronic)
Benign asbestos pleural effusion
Pulmonary embolism
Radiation therapy
Uremic pleurisy
Sarcoidosis
Postcardiac injury syndrome
Acute respiratory distress syndrome (ARDS)

Increased negative intrapleural pressure with accompanying pleural malignancy or inflammation
Lung entrapment
Cholesterol effusion (eg, due to tuberculosis, rheumatoid arthritis)
Connective tissue disease
Lupus pleuritis
Rheumatoid pleurisy
Mixed connective tissue disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Granulomatosis with polyangiitis (Wegener's)
Familial Mediterranean fever
Endocrine dysfunction
Hypothyroidism
Ovarian hyperstimulation syndrome
Lymphatic abnormalities
Malignancy
Chylothorax (eg, yellow nail syndrome, lymphangioleiomyomatosis, lymphangiectasia)
Movement of liquid from abdomen to pleural space
Pancreatitis
Pancreatic pseudocyst
Meigs' syndrome
Chylous ascites
Malignant ascites
Subphrenic abscess
Hepatic abscess (bacterial, amebic)
Splenic abscess, infarction
Miscellaneous
Pulmonary vein stenosis
Endometriosis
Drowning
Electrical burns
Capillary leak syndrome
Extramedullary hematopoiesis

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - **protein**: transudates - protein concentration below 3.0 g/dL (30 g/L)

  Tuberculous pleural effusions - total protein concentrations above 4.0 g/dL (40 g/L)

  Waldenström's macroglobulinemia and multiple myeloma – total protein concentrations range 7.0 to 8.0 g/dL (70 to 80 g/L)

  - **LDH**:

  empyema - LDH above 1000 IU/L (with upper limit of normal for serum of 200 IU/L)

  fluidothorax in Pneumocystis jirovecii pneumonia - pleural fluid/serum LDH ratio greater than 1.0 and a pleural fluid/serum protein ratio of less than 0.5

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - LDH:

  urinothorax - elevated pleural fluid LDH associated with low pleural fluid protein levels

  - cholesterol: derived from degenerating cells and vascular leakage from increased permeability

  cholesterol >250 mg/dL defines a cholesterol effusion (known as pseudochylothorax or chyliform effusion)

  - TAG:

  chylothorax – TAG in pleural fluid greater than 110 mg/dL

  TAG in an intermediate level between 50 and 110 mg/dL should be followed by lipoprotein analysis of the pleural fluid

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - glucose:

  low pleural fluid glucose concentration (less than 60 mg/dL, or a pleural fluid/serum glucose ratio less than 0.5): *rheumatic pleurisy*, complicated parapneumonic effusion, *empyema*, malignant effusion, TB pleurisy, lupus pleurits, esophageal rupture

  2 reasons: 1. decreased diffusion of glucose from blood to pleural fluid (rheumatoid pleurisy or malignancy)

  2. increased utilization of glucose by constituents of pleural fluid (neutrophils, bacteria, and malignant cells)

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - Creatinine - urinothorax - when a transudate has a pleural fluid/serum creatinine ratio >1

  - pH: normal pH 7.60 (due to a bicarbonate gradient between pleural fluid and blood)

  transudates - pH in the 7.40 to 7.55 range (urinothorax - pleural fluid pH <7.40)

  majority of exudates - pH range from 7.30 to 7.45

  Mechanisms responsible for pleural fluid acidosis (pH <7.30):

  1. increased acid production by pleural fluid cells and bacteria (empyema)
  2. decreased hydrogen ion efflux from the pleural space, due to pleuritis, tumor, or pleural fibrosis (malignancy, rheumatoid pleurisy, and TB pleurisy

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - pH: *pleural fluid acidosis* (pH <7.30) - diagnostic, prognostic, and therapeutic implications for patients with parapneumonic and malignant effusions

  malignant effusion: high initial positive yield on pleural fluid cytology, shorter survival, poorer response to chemical pleurodesis (strength not provide prognostic value for individual patients; not use as the sole criterion for the decision to forego pleurodesis. parapneumonic effusion (pH ≤7.15): pleural space drainage

  - amylase: acute pancreatitis, chronic pancreatic pleural effusion, esophageal rupture, malignancy (low discriminative value for differentiating benign from malignant effusions)

  - **adenosine deaminase** (ADA) – differentiate malignant (ADA 40 U/L) less than and TB effusion (ADA greater than 35 to 50 U/L) when exsudate is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative

Pleural fluid analysis

- **Chemical and biochemical analysis**

  - N-terminal pro-BNP, procalcitonin: not demonstrated sufficient diagnostic utility

- **Cytology**

  malignant pleural effusions - overall sensitivity 60% (may increase by 15% with the 2nd thoracentesis)

- **Cancer-related biomarkers**

  no single pleural fluid biomarker is accurate enough for routine use in the diagnostic evaluation of pleural effusion

Pleural fluid analysis

- **Nucleated cells -** total pleural fluid nucleated cell count is virtually never diagnostic Some settings in which the cell count may be helpful:

  1. complicated parapneumonic effusions, including empyema – cell counts above 50,000/microL

  2. exudates from bacterial pneumonia, acute pancreatitis, and lupus pleuritis - cell counts above 10,000/microL

  3. chronic exudates (TB pleurisy, malignancy) – cell counts below 5000/microL

  - acute pleural injury: early response neutrophilic, late mononuclear predominance

Pleural fluid analysis

- **Nucleated cells**

  - lymphocytosis (85-95%): TB pleurisy, lymphoma, sarcoidosis, chronic rheumatoid pleurisy, yellow nail syndrome, or chylothorax, some drugs (eg, dasatinib)

  malignant pleural effusions - lymphocyte-predominant in over one-half of cases (usually between 50 and 70%)

- **- eosinophilia (above 10%): PNO, h**emothorax, pulmonary infarction, benign asbestos pleural effusion, parasitic disease, fungal infection (coccidioidomycosis, cryptococcosis, histoplasmosis), drugs, catamenial pneumothorax with pleural effusion, malignancy (carcinoma, lymphoma, myeloma), TB pleurisy, parapneumonic effusions, chronic eosinophilic pneumonia

  - **mesothelial cells:** in small numbers in normal pleural fluid, prominent in transudates, and variable in exudate

  major clinical significance: TB pleurisy is unlikely if there are more than 5% of mesothelial cells

Thank you for your attention