Diagnosis

Symptoms

Weight loss: in 90% of patients.

Pain: in 80%.

Anorexia: in 60%.

Lethargy: in 40%.

Diabetes mellitus: in 15%.

Acute pancreatitis: atypical for patients to present with or develop acute pancreatitis (i.e., <5%)

Signs

Jaundice: in 85% of patients, often painless.

Cachexia: in 70%.

Hepatomegaly: in 60%.

Palpable gallbladder: Courvoisier's sign in 40%.

Epigastric mass: in 15%.

Ascites: in 10%.

Abdominal tenderness: in 5%.

Trousseau's syndrome: migratory thrombophlebitis in <1%.

Virchow's node: firm fixed node in left supraclavicular fossa in <1%.

Splenic-vein thrombosis: gastric fundus varices in <1%.

Investigations

Liver chemistry tests: to confirm "obstructive" jaundice; alkaline phosphatase often elevated and albumin low.

Clotting studies: prothrombin time may be prolonged but should correct after vitamin K, 10 mg i.m.

Complete blood count: to detect anemia or leukemoid reaction.

Serum marker analysis: *e.g.*, CA-19-9 (sensitivity 80%; specificity 90%); may be influenced by jaundice and have poor sensitivity for "early" pancreatic cancer [3].

Ultrasonography: to confirm dilated bile ducts and to localize disease (75% accuracy); increased detection of small tumors and better staging with endoscopic ultrasonography (90% accuracy).

Contrast-enhanced CT: 80%–90% accuracy [2].

Percutaneous biopsy: 80%–93% accuracy; should not be used in patients with potentially resectable tumors.

Endoscopic retrograde cholangiopancreatography: 90%–95% accuracy; brush or pancreatic juice cytology positive in 60%–70% of cases [1].

Laparoscopy: Often performed just before laparotomy to resect localized disease; resection for cure is typically abandoned if metastatic lesions are found at laparoscopyto detect small metastatic lesions otherwise missed [3].

Complications

Massive gastrointestinal hemorrhage: fair; caused by erosion into duodenum.

Gastric outlet obstructions/gastroparesis: common.

Pruritus: in 40%.

Acute cholangitis: in 2%.

Deep vein thrombosis: in 1%.

Differential diagnosis [4]

Obstructive jaundice
Bile-duct stones, ampullary tumor, tumors of the biliary tract, benign bile duct strictures, metastatic disease, duodenal cancer.

Hepatic jaundice
Chronic hepatitis, sclerosing cholangitis, congestive heart failure.

Cachexia
Gastric, colorectal, or ovarian cancer.

Other pancreatic disease
Chronic pancreatitis (may coexist), non-functioning endocrine tumors, metastases to pancreas.

Etiology

- The cause is largely unknown, but the following may have a role:

Smoking: relative risk, ~2.0 (compared with relative risk of lung cancer, ~20).

Diets high in total or animal fat.

Genetic predisposition (rare): familial colonic and pancreatic cancer, hereditary chronic pancreatitis, familial adenomatous polyposis, Peutz–Jeghers disease, von Hippel–Lindau disease, Lynch II, ataxic telangiectasia.

Long-standing chronic pancreatitis.

Epidemiology

- The incidence varies widely according to country and ethnicity, the highest incidences being in central and northern Europe, North America, and Australasia.
- The incidence standardized by age is 8–11 in 100 000 women and 10–12.5 in 100 000 men.
- Pancreatic cancer occurs less in premenopausal women, but the difference between men and women decreases with age.
- The mean age of presentation is 67 years for women and 63 years for men.

Pathology

- 70%–80% of pancreatic cancers arise in the head of the gland, the rest in the body or tail or diffusely located; <6% are multicentric.

Duct cell origin: 95%.

Acinar cell origin: 2%.

Uncertain histogenesis: 2%.

Nonepithelial tumors: 1%.

Treatment

Diet and lifestyle

- Abnormal gastric emptying results in malnourishment and dehydration in most patients.
- Parenteral nutrition does not alter the course of unresectable disease.

Pharmacological treatment

Before surgery or endoscopy

- The following are needed initially before resection or relief of jaundice:

Correction of anemia, optimization of nutritional status.

Vitamin K, 10 mg i.m. daily for 3 days if prothrombin time is prolonged.

Crystalloid solution, 1–2 L i.v. for at least 24 hours before any procedure.

For any procedure requiring instrumentation of the biliary tract.

Palliative chemotherapy for unresectable disease.

Chemotherapy offers very modest benefits in survival and variable impact on quality of life.

When used, regimens using 5-fluorouracil or gemcitabine are most common [6,7].

Radiation may enhance the value of chemotherapy.

For pain

- In many patients, the disease is so advanced that conservative management is most appropriate (*i.e.*, pain relief and palliative care).
- NSAIDs may precipitate acute renal failure, gastropathy.
- Patients can be given morphine slow-release orally, i.v., or by epidural infusion using a portable pump; this may cause constipation, nausea, and drowsiness.
- Metoclopramide hydrochloride (10 mg every 8 hours oral or i.v.) may be used for nausea, although benefits are often limited.

Chemotherapy [5]

- Gemcitabine has been shown to produce clinical benefit, improved survival, and increased time to disease progression in patients with locally advanced or metastatic disease.

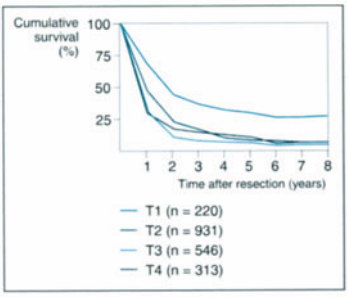
Standard dosage	1000 mg/m² i.v. infused over 3 minutes weekly.
Contraindications	Known hypersensitivity to gemcitabine; pregnancy.
Main drug interactions	None of significance.
Special points	Prolongation of infusion over 60 minutes may increase toxicity.
Main side effects	Myelosuppression, nausea, vomiting, elevated hepatic transaminases.

Nonpharmacological treatment

- Treatment choice for jaundice depends on age, tumor burden, and local expertise.
- In-hospital mortality figures are comparable for the different techniques, although endoscopic methods are probably superior.
- Potential surgical candidates must be appropriately staged, with the help of a radiologist and surgeon.

Surgical resection

- Resection is possible in 10%–15% of patients, with a hospital mortality of 3%–10% [6].



Survival rates after resection for pancreatic cancer stages T1–T4, based on data from the Japanese Pancreatic Cancer Registry.

Endoscopic stents

- Stents are most useful in patients with symptoms caused by biliary tract obstruction.
- Expandable metal stents need fewer changes and are recommended for patients with an expected better survival rate [7].

Percutaneous internal stenting

- The complication rate is higher than for endoscopic stents.

Surgical bypass

- Duodenal bypass may be used to avoid obstruction from growth into duodenum.

Treatment aims

To relieve jaundice, duodenal obstruction, weight loss, and pain.

Prognosis

- Cure is rarely possible, but a drainage procedure often results in the best palliation.
- After palliative treatment, mean survival is 3–6 months.
- After resection, mean survival is 12–18 months, and the 5-year survival rate is 5%–15%; the survival rate may be increased by adjuvant radiochemotherapy.

Follow-up and management

- Patients who have had resection may be suitable for postoperative adjuvant external beam radiotherapy followed by chemotherapy for 6–24 months.
- After palliative treatment, stents may need to be changed, gastric bypass may be needed for duodenal obstruction, and patients may need pain control.
- Localized recurrence may be worth re-resecting in some patients.

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Pancreatitis, acute

Diagnosis

Symptoms

Epigastric pain: sudden onset; radiation into back (relative relief obtained by sitting forward or curling into a "fetal position"); may become increasingly severe.

Anorexia, nausea, vomiting.

Fever: less common.

Signs

Tachycardia, diaphoresis, peritoneal signs, hypotension, tachypnea: suggests more severe disease.

Ecchymosis: on flanks (Turner's sign) or periumbilically (Cullen's sign); often cited but rarely seen signs of intra-abdominal hemorrhage secondary to pancreatitis.

Peripheral fat necrosis: uncommon (more frequent in alcohol-induced pancreatitis).

Jaundice: especially in gallstone-induced pancreatitis.

Tetany: secondary to hypocalcemia.

Investigations

Amylase measurement: abnormal serum concentration (*e.g.*, >100 IU/dL); elevated lipase more specific and sensitive (both may be falsely elevated in renal failure).

Serum transaminase, alkaline phosphatase, and bilirubin measurement: elevations increase the possibility of biliary pancreatitis.

Complete blood count: to evaluate for anemia and systemic evidence of inflammation.

Serum creatinine, serum calcium: in toxic patients.

Serum lipids: in patients with unexplained pancreatitis.

Ultrasonography: to determine as soon as possible whether gallstones are causative (~80% sensitive); useful in following course of acute fluid collections (*i.e.*, pseudocysts and abscesses).

Arterial blood gases: in patients with tachypnea, shock; hypoxia indicates poor prognosis.

Contrast-enhanced CT: useful to determine extent of interstitial pancreatitis vs. necrotizing pancreatitis; done early in patients with severe presentation or in patients slow to respond to conservative therapy.

Fine-needle aspiration: to sample necrotic tissue for Gram stain and culture to ascertain presence of infected tissue.

Endoscopic retrograde cholangiopancreatography (ERCP): acutely for patients with biliary pancreatitis to remove obstructing stones from the bile duct or ampulla of patients suspected of having traumatic rupture of the pancreatic duct and traumatic pancreatitis. ERCP may aggravate acute pancreatitis and should be performed with caution to ascertain presence of gallstones of choledocholithiasis requiring endoscopic extraction and other causes in biliary tree or pancreas; in severe pancreatitis, disruption of main pancreatic duct suggests significant central necrosis; also indicated in cases of pancreatic trauma.

Complications

Anemia, hypoglycemia, hypocalcemia.

Acute fluid collections: occur early, in 30%–50% with severe disease and often in patients with mild disease; only 33%–50% of these become clinically significant pseudocysts.

Pancreatic necrosis: clinically significant in 3%–5%; up to 70% are infected necrosis; lesser degrees (<30% of the gland) often occur in clinically mild pancreatitis.

Hemorrhage: splenic artery aneurysm (an uncommon but particularly serious complication).

Multiorgan failure: acute respiratory distress syndrome, renal failure, disseminated intravascular coagulation, metabolic acidosis.

Sepsis.

Differential diagnosis

Abdominal catastrophe: any perforation of gastrointestinal tract, ruptured aneurysm, ectopic pregnancy, mesenteric infarction, ovarian cyst torsion.

Pyelonephritis, renal colic.

Peptic ulcer disease.

Cholangitis, cholecystitis.

Splenic infarction.

Ruptured esophagus (Boerhave's syndrome).

Crohn's disease.

Etiology

Alcohol in >50%.

Biliary disorders in 30%–60% of patients: gallstones, cholesterolosis, "sludge," ascariasis, sclerosing cholangitis, choledochocele, tumors.

Complication of endoscopic retrograde cholangiopancreatography.

Penetrating duodenal ulcer.

Hyperlipidemia in 1%–5%: types I (30%), IV (15%), and V (30%–40%).

Unusual causes in 1%–5%: obstructive (pancreas divisum, strictures, tumors), trauma, ischemia, infections (viruses), drugs (azathioprine, L-asparaginase, warfarin), vasculitides, transplantation, hypercalcemia, scorpion bites [2].

Epidemiology

- Gallstone-induced pancreatitis occurs more often in elderly people and women.
- Typically, 30–60 in 10^5 population are affected annually.
- The incidence is increasing.

Treatment

Diet and lifestyle

• During acute illness, patients should not ingest liquids or solids.

• Once pancreatitis has resolved, patients must eat regular meals; prolonged starvation followed by large meals must be avoided; clinical symptoms, rather than serum amylase or lipase levels, should determine when the patient may begin eating.

• Refraining from alcohol must be stressed to patients with alcohol-related pancreatitis.

Pharmacological treatment

• Supportive care involves the following:

Intravenous fluid: crystalloid and colloid (up to 12 L may be sequestered outside of the vascular compartment in the first 24–48 hours).

Pain relief with narcotics such as meperidine (50–100 mg i.m. every 4–6 hours).

Calcium supplementation as needed for patients with hypocalcemia and tetany.

Monitoring and treatment of diabetes mellitus as needed.

Pressor support: if systolic blood pressure <90 mm Hg or renal perfusion inadequate despite fluid replacement.

Antibiotics: for patients with gallstone pancreatitis.

• Glucagon, antiproteases (*e.g.*, aprotinin), somatostatin, are probably of no value in the setting of severe pancreatitis.

Nonpharmacological treatment

Nasogastric suction only for symptomatic relief of nausea and vomiting.

Oxygen administration: if oxygen saturation in arterial blood <90%; large pleural effusions should be drained.

Hemodialysis: for renal failure refractory to fluid replacement and inotropic support.

Endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy: for patients with severe pancreatitis in whom biliary tract disease (*i.e.*, biliary pancreatitis) is suspected.

Infected necrosis is a strong indication for surgery; patients who do not improve or who deteriorate over 5–10 days of conservative therapy should undergo CT scanning with needle aspiration of any regions suspicious for infection.

Drainage: for large pseudocysts (>6 cm), persisting in size, expanding, or causing symptoms; repeated percutaneous tapping increases risk of infection and abscess; internal cyst drainage via endoscopically placed stent or surgery is preferred to external drainage; abscess or infected necrosis must be treated early and aggressively preferably with surgical drainage [3,4].

Treatment aims

To provide supportive care.

To prevent further attacks.

To reduce complications and underlying disorders (e.g., hyperlipidemia).

Prognosis

• Ranson's criteria of severity is predictive of mortality.

• Most patients recover after management in hospital with fluid replacement.

• Recurrent attacks are highly probable if alcohol abuse continues or if hyperlipidemia is not treated.

• Unless cholecystectomy or endoscopic sphincterotomy is performed in patients with gallstones, 10%–40% suffer recurrent attacks [2].

Follow-up and management [5]

• Further attacks can be prevented by laparoscopic cholecystectomy (for gallstones) or endoscopic sphincterotomy, stopping alcohol intake, treating hyperlipidemia and other underlying disorders.

• Follow-up is needed in patients in whom the cause has not been identified or treated or in those who have had extensive surgery for necrosis.

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Pancreatitis, chronic

Diagnosis

Symptoms

• Chronic pancreatitis usually evolves over 5–20 years; symptoms, signs, and complications vary during this period [1].

Abdominal pain: in 90% of patients; often worse with eating; acute pancreatitis in 40%.

Weight loss: in 80%.

Diarrhea or steatorrhea: in 40%.

Polyphagia, polydipsia of diabetes mellitus: in 40%.

Signs

Greasy stool: in 10% on rectal examination.

Epigastric mass: in 10%.

Anemia: nonspecific anemia of chronic disease.

Jaundice: suggests biliary stricture from chronic pancreatitis.

Muscle wasting, cachexia, ecchymosis: malnourishment and evidence of malabsorption (*e.g.*, inability to absorb vitamin K) seen in patients with advanced disease.

Investigations

Serum amylase, lipase measurement: concentrations raised in acute exacerbation of pancreatitis; often normal in chronic pancreatitis.

Blood glucose measurement: at least 20% of functional parenchyma is required for euglycemia.

Abdominal radiography: pancreatic calcification has high specificity for chronic pancreatitis but limited sensitivity.

72-hour fecal fat collection: excretion of >6 g fecal fat/24 hours in patients ingesting at least 100 g of fat per day in the absence of other causes of malabsorption is highly suggestive of chronic pancreatitis.

Ultrasonography: for parenchymal changes, duct dilatation, calcification, pseudocysts, ascites; endoscopic ultrasonography is particularly good at rendering a diagnosis of chronic pancreatitis.

Contast-enhanced CT: highly sensitive for calcification; also useful to evaluate for inflammatory mass, ductal dilation, pseudocysts, ascites.

Pancreatic function tests: collection of pancreatic secretions via a nasogastric tube following stimulation by i.v. secretin or cholecystokinin; reduced lipase, bicarbonate, proteolytic enzymes confirms the presence of exocrine pancreatic insufficiency.

Endoscopic retrograde cholangiopancreatography: for changes in main duct and side branches ("minimal change pancreatitis"), stones (calcified and noncalcified) and protein plugs in duct, pseudocysts, fistulas.

Complications

Pancreatic exocrine insufficiency.

Pancreatic endocrine insufficiency.

Duodenal ulcer.

Common bile duct obstruction: secondary biliary cirrhosis (rare).

Duodenal obstruction.

Pseudocysts: pancreatic, intra-abdominal, mediastinal.

Pancreatic ascites.

Pleural effusion.

Pancreatic abscess.

Pancreatic pseudoaneurysm.

Splenic vein thrombosis: gastric fundus varices.

Narcotic dependency.

Differential diagnosis

Recurrent acute pancreatitis without chronic pancreatitis.

Idiopathic hypertrophy of head of pancreas.

Secondary pancreatic inflammation (duodenal ulceration).

Pancreatic cancer.

Celiac disease.

Bacterial overgrowth of small bowel.

Etiology

Alcohol in 60%–80% of patients.

Obstruction in 10%: ampullary stenosis, pancreas divisum, annular pancreas, stricture (trauma, tumor), irradiation, pancreatitis.

Idiopathic in 10%.

Hereditary (chronic familial pancreatitis).

Malnutrition (tropical pancreatitis).

Cystic fibrosis.

Tropical pancreatitis.

Epidemiology

• In industrialized countries, the incidence largely depends on alcohol consumption (other factors have a modifying effect): 1–10 in 100 000 population are affected annually.

• Chronic pancreatitis occurs more often in men than in women; the ratios vary from 10:1 to 2:1.

• The incidence is increasing in all countries.

Treatment

Diet and lifestyle

- Patients should eat regular meals and abstain from alcohol.
- Use of medium-chain triglycerides is occasionally helpful for patients with malnutrition and extensive fat malabsorption.

Pharmacological treatment

- When possible, therapy should be directed at the underlying cause.

For exocrine insufficiency: pancreatic enzyme therapy consisting of 28 000 IU of lipase administered with meals and titrated to control symptoms (steatorrhea, weight loss); concomitant gastric acid reduction (*e.g.*, with an H_2-receptor antagonist or proton pump inhibitor) may improve the activity of enzyme supplements [2].

For endocrine insufficiency: insulin therapy is usually required to control diabetes.

For pain

- Self-titration of pancreatic supplements containing proteases may reduce mild or moderate pain (despite the absence of overt steatorrhea) [3].
- Simple analgesics or NSAIDs can be used; however, patients often require management with narcotics.
- Celiac plexus block with alcohol can be considered, repeated if necessary.

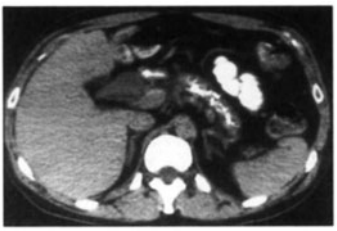
Nonpharmacological treatment

Main pancreatic duct drainage

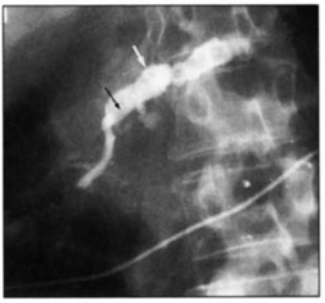
- Endoscopic sphincterotomy and stone extraction are suitable in only a few patients; stenting of strictures or pancreatic sphincterotomy may be helpful in select cases [4].
- Pancreaticojejunostomy or transduodenal sphincteroplasty are alternatives to endoscopic treatment; draining alone is usually insufficient in the presence of extensive parenchymal calcification, inflammation, and pain [5–8].

Surgery for pain

- Surgery can be considered in patients with intractable pain.
- For nondiabetic patients or those having an operation for the first time, treatment should be conservative and only "dominant" disease resected.
- For patients with diabetes or previous surgery, extensive surgery may be required.
- Preservation of the stomach, pylorus, duodenum, and spleen is almost always possible.



CT scan reveals numerous pancreatic stones in patient with chronic alcholic pancreatitis. Pancreas appears atrophic.



Endoscopic retrograde cholangiopancreatography reveals dilatation of main pancreatic duct (*white arrow*). There are numerous introductal calculi (*black arrow*).

Treatment aims

To eliminate the underlying cause.
To relieve pain.
To delay disease progression (duct drainage).
To treat malabsorption.

Prognosis [4]

- The disease is not always progressive.
- Pain and calcification occur after 5–10 years, and both may subsequently regress, but this is unpredictable.
- The long-term survival is often poor (~50% of patients die within 7 years) because of comorbid factors.
- Preservation of the quality of life and chronic pain management are the biggest challenges of dealing with this group of patients.

Follow-up and management

- All patients must be followed up to monitor endocrine and exocrine function and pain and to ascertain the need for operation or reoperation.

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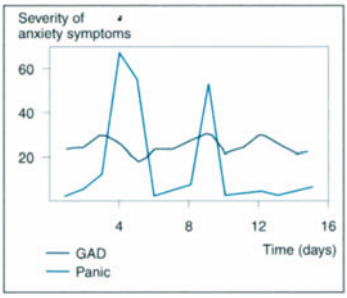
Diagnosis

Symptoms

Panic

Recurrent attacks of severe unprovoked anxiety: starting suddenly, reaching a peak within a few minutes, and lasting at least 20 minutes, with at least four of the following:

Palpitations.
Stomach churning.
Hot or cold flushes.
Shaking or trembling.
Choking or difficulty breathing.
Fear of dying.
Feelings of unreality.
Fear of losing control.
Sweating.
Chest pain or discomfort.
Feeling dizzy, unsteady, lightheaded, or faint.
Paresthesias (numbness or tingling sensations).



Course of pure panic disorder and pure generalized anxiety disorder (GAD).

Generalized anxiety disorder (GAD)

Relatively persistent anxiety: at least 6 months, associated with worrying and apprehension about events and other matters that do not justify excessive worry; the anxiety and worry are associated with at least three of the following symptoms:

Restlessness: feeling keyed up or on edge.
Being easily fatigued.
Difficulty concentrating or mind going blank.
Irritability.
Muscle tension.
Sleep disturbance: difficulty falling or staying asleep or restless, unsatisfying sleep.

Signs

Panic

• Physicians seldom see a panic attack in vivo because patients usually feel more secure in a medical setting. Features present on examination include the following:

Fear of having a panic attack.
Reassurance that a heart attack or other physical catastrophe is not imminent.
Wish to be physically examined.
Physiological evidence of anxiety: usually no different from generalized anxiety disorder.

Generalized anxiety disorder

Furrowed brow, hunted look, lack of confidence: evidence of long-standing anxiety.
Tachycardia: pulse 80–100 beats/min.
Sweating.
Dilated pupils.
Observed tremor.

Investigations

• Investigations should not be entered into lightly in patients with anxiety disorders because they may cause hypochondriacal concern and increased anxiety. If, however, anxiety appears for the first time in middle age or later, it may have an organic cause.

Thyroid function tests, complete blood screening, neurological assessment: may sometimes be indicated if anxiety is episodic, diurnally varied, or linked to specific somatic symptoms persistently; epilepsy and pheochromocytoma are rare but remediable causes of anxiety.

Complications

Alcohol dependence: with persistent anxiety (alcohol provides temporary relief).
Hypochondriasis: due to anxiety about bodily complaints.
Agoraphobia: due to persistent severe anxiety, particularly after panics in public places.
Social phobia: due to self-consciousness of anxiety attacks.

Differential diagnosis

Tachycardia, pulmonary emboli, organic dyspnea, thyrotoxicosis: anxiety related to physical disease.
Mixed anxiety and depressive disorder, depressive episode: anxiety due to depressive symptoms.
Posttraumatic stress: anxiety due to major unusual event (e.g., rape, major disaster).
Hypochondriasis, somatoform disease: anxiety due entirely to fear of disease or preoccupation with bodily symptoms.
Organic psychoses, schizophrenia, affective psychoses: anxiety due to psychotic symptoms, e.g., delusions or hallucinations.
Agoraphobia, social or simple phobias: anxiety due to specific stimuli, accompanied by avoidance of the stimuli.
Most GAD in the elderly is caused by depression.
Substance abuse disorders: anxiety due to alcohol or drug abuse.

Etiology

• The immediate cause of anxiety in panic and generalized anxiety disorder is unknown.
• The episodes of anxiety are unfocused or "free-floating" (generalized anxiety disorder) or spontaneous (panic).
• Both disorders are associated with life changes and events and may sometimes be a delayed reaction to the events.
• A genetic component is possible.

Epidemiology

• Panic attacks are most frequent in the 15–24-year age range and have an annual prevalence of ~2% in this group, with ~1% in the total population.
• Generalized anxiety disorder is much more common, with an annual prevalence of ~6%.
• Major depression coexists with generalized anxiety disorder and panic disorder in up to 60% of patients.

Treatment

Diet and lifestyle

• A good square meal is sometimes said to be the best tranquillizer in the world; unsurprisingly, therefore, some anxious people resolve their anxiety by overeating and getting fat. This may relieve their anxiety (good studies show that fat people are less anxious generally than thin people) but does not improve their health overall.

• Because anxious people fear trouble around every corner, they often restrict their lifestyles; this is seen to its extreme in the housebound agoraphobic.

Pharmacological treatment [1]

• The patient's view must be taken into account: some refuse drug treatment, others are equally negative about psychological treatment.
• Less effective treatments, *e.g.*, beta-blockade and relaxation training, should be avoided in patients with panic disorder.
• Combined drug and psychological treatments are acceptable and may even be more effective than individual treatments alone.
• Patients must be warned against self-medication with alcohol for anxiety and pain: it provokes worse symptoms in the longer term.
• The duration of treatment should be set in advance, whenever possible.

Standard dosage	Specific 5-HT reuptake inhibitors, e.g., paroxetine, 20-60 mg daily [2]. Benzodiazepines, e.g., clonazapam 0.5 mg twice daily; alprazolam, 0.25-6.0 mg daily. Buspirone, 10-60 mg daily, especially useful for eldery patients [3]. Beta-blockers, e.g., propranolol, 40-120 mg daily. Heterocyclic antidepressants, e.g., clomiprimine, 100-150 mg daily [1].
Contraindications	Benzodiazepines: caution with previous or current evidence of dependent personality or behavior or substance abuse.
Special points	*Serotonin reuptake inhibitors:* first-line agents, effective in most forms of anexity disorders [2]. *Benzodiazepines:* rapid and more effective in short term than other treatments, but tolerance and dependence make them generally unsuitable for regular treatment; may interfere with success of behavior therapy. Beta-blockers: useful if somatic symptoms of anxiety are prominent but not severe (more useful in generalized anxiety disorder). *Heterocyclic antidepressants:* more effective than benzodiazepines when given for more than 4 weeks, but slow onset of antianxiety effects.
Main drug interactions	Additive effects with alcohol.
Main side effects	Sedation (not beta-blockers).

Nonpharmacological treatment

Psychological treatments [1]

Relaxation training: of some value (but less than other more intensive therapies) and can be very cheap.

Cognitive therapy: effective in both disorders, may be superior to other psychological treatments; substantially decreases relapse rates after medication taper; aimed at altering unproductive dysfunctional thinking that helps to generate and maintain anxiety; patients with panic disorders learn to decatastrophize thinking, so that attacks are avoided.

Behavior therapy: effective in treating maladaptive behaviors associated with anxiety, mainly by gradual exposure to more adaptive situations.

Combination therapies: cognitive behavior therapy, anxiety management training.

Hypnosis and alternative therapies (yoga, meditation): sometimes useful but not as effective as cognitive and behavior therapies.

Treatment aims

To alleviate symptoms.
To teach patient to recognize anxiety early.
To teach patient stress management and relaxation techniques.

Prognosis

• Prognosis is generally good except when symptoms begin early in adult life and are associated with personality disturbance.
• Markers of poor prognosis in panic disorder include coexisting depression, severe symptoms, and agorophobia.

Follow-up and management

• Drug treatment is best regarded as a temporary measure, except in patients who are persistently anxious; long-term treatment should be psychological because relapse is less likely and self-esteem is improved.

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3. Folles DG, Fuller WC: Anxiety disorders and insomnia in geriatric patients. *Pychiatric Clin North Am* 1997, **29(1)**:137–164.

Diagnosis

Symptoms

Tremor: in ~70% of patients; unilateral and usually noted in hand first; may be seen in jaw or leg. Most often unilateral at onset.

Poverty of movement, difficulty initiating movements and with repetitive movements: *e.g.*, shuffling gait, drooling, difficulty turning in bed, micrographia, softness of voice, constipation.

Rigidity: *e.g.*, poor balance, falls, muscle stiffness, pain.

Signs

Tremor: asymmetric, resting, "pill-rolling" at 3–5 Hz; usually disappears on intention; increased by anxiety; possibly postural tremor at 6–8 Hz.

Rigidity and bradykinesia: stooped, flexed posture; shuffling gait with poor swing of affected arm; cogwheel rigidity, may be enhanced by synkinesis; immobile facies, reduced blink and swallowing rates; rigidity usually noted first in axial muscles, *e.g.*, neck and shoulder.

Investigations

• No tests are available for Parkinson's disease; the diagnosis is based on clinical features alone.

• Investigation is indicated when the diagnosis is in doubt or presentation is atypical, especially in young-onset cases.

Testing of autonomic function: patients with multiple system atrophy may show abnormalities.

MRI: can show abnormal hypointensity in the putamen of patients with multiple system atrophy, can reveal strokes in some patients with parkinsonism.

Copper and ceruloplasmin measurement: in all patients with young-onset or atypical Parkinson's disease.

Huntington's genetic testing: for young presentation with family history.

Complications

Depression, anxiety.

Postural imbalance: with falls and trauma.

Cognitive and psychiatric problems: frontal lobe dysfunction, bradyphrenia, fluctuating confusional state (dementia in 25% of patients); possible overlap with other syndromes, *e.g.*, diffuse Lewy body disease, senile dementia of Lewy body type.

Complications of L-dopa: dyskinesias, motor fluctuation.

Differential diagnosis

Drug-induced parkinsonism: *e.g.*, phenothiazines, butyrophenones; usually symmetrical and reversible.

Essential tremor: bilateral; absent at rest, exacerbated by intention, or maintaining posture; improved by alcohol; possible family history; should be treated with beta-blockers or primidone when necessary.

Multiple system atrophy or progressive supranuclear palsy: symptoms and signs usually symmetrical; tremor less usual; falls frequent; additional features, *e.g.*, pyramidal or cerebellar deficits, gaze palsies, or autonomic involvement including postural hypotension, and bladder dysfunction.

Wilson's disease: 40% present with neurological features, mainly parkinsonism and hypokinetic dysarthria; liver cirrhosis or psychiatric disease also occur; Kayser–Fleischer rings visible by slit lamp in most; low serum ceruloplasmin, high urinary copper; liver biopsy shows high copper and evidence of liver cell damage; should be treated with penicillamine.

Toxin-induced parkinsonism (*e.g.*, carbon monoxide).

Mitochondrial disorders; abnormal movements, usually dystonia or chorea.

Etiology [1]

• >80% dopamine depletion occurs in the striatum at presentation; neurons are lost in the substantia nigra (dopaminergic), locus caeruleus (noradrenergic), and substantia innominata (cholinergic). Intracytoplasmic inclusions, Lewy bodies, are found in surviving neurons.

• The cause of Parkinson's disease is not known, but environmental toxins and genetic susceptibility may play a role alone or in combination.

Epidemiology

• The incidence is ~20 in 100 000, with an overall prevalence of 150 in 100 000 (500 in 100 000 for those aged >50 years).

• The male : female ratio is equal.

• Younger-onset patients tend to develop more motor fluctuations, and older-onset patients have a much higher incidence of associated dementia.

Treatment

Diet and lifestyle

• Maintaining activity is important: a multidisciplinary approach, with physical therapy, occupational therapy, speech therapy, and social work contact is helpful; patients and caregivers may need support.

• Dietary protein should be reduced during the day; a main meal at night allows more predictable absorption of L-dopa.

Pharmacological treatment [2]

At diagnosis

• Most neurologists advocate selegiline or dopamine agonists.

Standard dosage	Selegiline (Eldepryl). 5 mg twice daily.
Contraindications	Possible interaction with tricyclic antidepressants or 5-HT reuptake inhibitors.
Special points	May delay requirement for L-dopa, although mechanism of action uncertain; some symptomatic benefit.
Main drug interactions	Concurrent L-dopa dose may need to be decreased 20%–50%; should not be administered with tricyclic antidepressants.
Main side effects	Gastrointestinal upset, hypotension, confusion.

At review

• Treatment is essentially symptomatic.

• L-Dopa is prescribed when clinical features interfere with life, or postural instability is noted on examination.

• Tremor and bradykinesia respond well.

• The use of controlled-release L-dopa offers some improvement in patients with medium to advanced disease, especially in decreasing "off time"; transition to these drugs should be gradual because the bioavailability is different from that of the standard preparations; some neurologists use controlled-release preparations early to provide a more "physiological" prolonged drug exposure to dopaminergic neurons.

• Dopaminergic agonists may be used alone (early) or in combination with L-dopa.

Standard dosage	L-Dopa with a dopa decarboxylase inhibitor, initially at low dose and frequency, *e.g.*, 100 mg twice or 3 times daily, increased as necessary. Dopaminergic agonists, *e.g.*, bromocriptine or pergolide in low doses initially and built up gradually.
Contraindications	*L-Dopa:* closed angle glaucoma. *Dopaminergic agents:* hypotension, cardiac arrhythmias.
Special points	*L-Dopa:* generally, frequent small doses (up to every 2–3 hours) are better than infrequent large doses. *Dopaminergic agents:* may be used alone, but tolerance to these drugs develops quickly.
Main drug interactions	*Dopaminergic agents:* combination with L-dopa may improve control.
Main side effects	*L-Dopa:* gastrointestinal upset, postural hypotension, confusion, hallucination, dyskinesias and dystonia; neuropsychiatric side effects best treated by dose modification, but clozapine or olanzapine may be used (possible development of agranulocytosis). *Dopaminergic agents:* hypotension, hallucinations, confusion, gastrointestinal symptoms.

• Amantidine or anticholinergics may be useful adjunctive medications for tremor.

Treatment aims

To improve functional disability.

To avoid or minimize drug-related side effects.

To treat fluctuations when present.

Other treatments

• Posteroventral pallidotomy may be useful in selected patients to improve dyskinesias and motor fluctuations.

Prognosis

• Parkinson's disease progresses at variable rates.

• Patients with dementia have a significantly worse prognosis.

Follow-up and management

• The need for symptomatic treatment should be assessed.

• Correct use and titration of drugs should be monitored.

• Medical and support needs should be assessed.

Key references

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2. Marsden CD: Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1994, **57**:672–681.

Parvovirus B19 infection

Diagnosis

Symptoms

• Often no symptoms are manifest.

Mild feverish illness: in children.

Mild feverish illness with arthralgia or arthritis: in adults.

Symptoms of an aplastic crisis: in patients with hemolytic anemias or occasionally normal people; onset usually acute but self-limiting.

Symptoms of persistent severe anemia: in immunosuppressed patients.

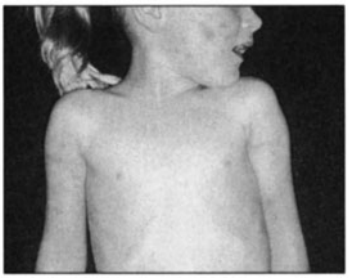
Signs

• The illness, when accompanied by a rash, is known as erythema infectiosum, fifth disease, or slapped-cheek syndrome.

Rash: usually seen in children; appears on cheeks, giving slapped-cheek appearance; lasts 1 week; recurs for several months on exposure to sun or wind; variable but often reticular maculopapular rash may also develop on arms and legs but rarely affects palms or soles.

Lymph-node enlargement: in adults.

Arthralgia or arthritis: often involving wrists and knees in adults; can occur without rash; usually last 2–4 weeks, occasionally longer.



Slapped-cheek appearance of parvovirus B19 infection and reticular rash on arms. (*See* Color Plate.)

Investigations

Serology: IgM specific to parvovirus B19 manifest in early illness; parvovirus B19 IgG antibody develops early in illness and falls within 1–2 months.

Complications

Aplastic crisis.

Fetal anemia, hydrops fetalis, and death: especially during second trimester, although effect on pregnancy uncertain; about one-third of pregnant women with primary infection transmit it to fetus.

Differential diagnosis

Scarlet fever: parvovirus has no oral stigmata.

Measles: no Koplik's spots or marked syndrome in parvovirus infection.

Rubella, enteroviral infections, cytomegalovirus, Epstein–Barr virus, toxoplasmosis.

Etiology

• Infection is by parvovirus B19.

• Transmission is by respiratory droplets.

Epidemiology

• Infection occurs worldwide.

• Most infections are in spring or early summer.

Infectivity

• Parvovirus B19 is moderately infective.

• Immunity is apparently for life after an acute episode.

Mean incubation period

To the mild febrile illness: 6–8 days.

To the rash: 17–18 days.

Treatment

Diet and lifestyle

• People known to be infected should avoid contact with pregnant women.

Pharmacological treatment

Analgesics, *e.g.*, acetaminophen.

NSAIDs for reactive arthralgia.

Treatment aims

To relieve symptoms (if any).

Prognosis

• Prognosis is good in acquired illness.

• Mortality is 9% in recognized fetal infections.

Follow-up and management

• Follow-up is not needed.

General references

Brown KE, Young NS: Parvovirus B19 in human disease. *Am Rev Med* 1997, **48**:59–67.

Gay NJ, *et al.*: Age specific antibody prevalence to parvovirus B19: how many women are infected in pregnancy? *Comm Dis Rep* 1994, **4**:R104–R107.

Levy R, Waissman A, Blomberg G, Hagay ZJ: Infection by parvovirus B19 during pregnancy: a review. *Obstet Gynecol Surv* 1997, **52**:254–259.

Pattison JR: Human parvovirus B19. *BMJ* 1994, **308**:149–150.

Diagnosis

Symptoms

Pericarditis

Mild to severe precordial pain: on inspiration or worse on inspiration; may radiate to neck and shoulders; worse on coughing, swallowing, or sneezing; improved by leaning forward.

Dyspnea, nausea.

Tamponade

Precordial discomfort: occasionally, due to large effusions.

Cough, hoarseness, tachypnea, dysphagia: due to pressure.

Malaise, cyanosis, dyspnea, sweating, anxiety, hypotension: rapidly developing.

Signs

Pericarditis

Fever.

Pericardial, often pleuropericardial, coarse rub: best heard at left sternal edge with patient leaning forward; may come and go over minutes to hours, may decrease with development of effusion.

Initially normal venous pressure.

Tamponade

Tachycardia: nearly always present.

Low blood and pulse pressures.

Pulsus paradoxus: pulse may disappear on inspiration; may also occur in asthma.

Raised venous pressure: with prominent "y" descent and no "x" descent; may increase on inspiration.

Investigations

• For any pericardial disease, the underlying cause must always be sought.

Pericarditis

Complete blood count, ESR and urine and electrolyte measurement. TSH and T4 to exclude hypothyroidism.

Antistreptolysin O titer, antineutrophil factor, rheumatoid factor analysis. HIV test to exclude AIDS and fungal serology in immunocompromised patients or in endemic areas.

Cardiac enzyme tests: enzymes may be normal or increase, but creatinine phosphokinase MB and troponins probably not significantly increased unless accompanying myocarditis.

Paired viral antibody screening: increase in neutralizing antibodies (up to 4 times) within 3–4 weeks of onset.

Mantoux test.

ECG: changes throughout all leads; raised ST segment, PR depression, inverted T waves only in some patients, pericardial effusion (low-voltage QRS and T wave in large effusions), electrical alternans (caused by heart swinging about).

Chest radiography: normal unless pericardial fluid >250 mL; cardiac contour may be globular, with no congestion in the lungs.

Tamponade

Echocardiography: essential in any patient in whom pericardial fluid is suspected (*e.g.*, cardiomegaly on chest radiography with hypotension); right ventricular collapse characteristic of tamponade.

Complications

Relapsing or constrictive pericarditis, pericardial effusion and tamponade: complications of pericarditis.

Hypotension, renal failure: complications of tamponade.

Differential diagnosis

Pericarditis

Extension of infarct after acute myocardial infarction.

Myocardial infarction, unstable angina, ulcer dyspepsia, acute aortic dissection, spontaneous pneumothorax, pleurisy, pulmonary embolus.

Tamponade

Cardiomyopathy or constrictive pericarditis.

Etiology

Pericarditis

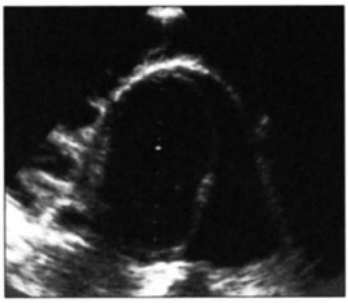
Viral: may be associated with pleurisy.
Autoimmune or collagen vascular diseases: SLE, scleroderma.
Rheumatic fever, rheumatoid athritis.
Myocardial infarction or cardiac surgery.
Metabolic: uremia, myxedema.
AIDS, opportunistic infections (*e.g.*, tuberculosis).
Association with neoplasia, particularly lymphoma, leukemia, carcinoma of bronchus or breast.

Tamponade

Any of the above, but particularly the following:
Carcinoma of bronchus or breast.
Uremia.
Cardiac surgery.
Viral infection (in young patients).

Epidemiology

• The incidence at postmortem examination is 2%–6%.
• The clinical incidence is <1 in 100 hospital admissions.
• More men than women are affected.
• The disorder may recur after treatment but is usually a one-off event, depending on the cause.



Pericardial space containing fluid (*top center*); bright pericardium (*mid center*); left ventricle (*lower center*); fibrinous strands in pericardial fluid (*lower left*).

Treatment

Diet and lifestyle

- No special dietary precautions are necessary.
- Overactivity is contraindicated until the symptoms have resolved.

Pharmacological treatment

- Drugs are used for pericarditis to decrease inflammation and treat the underlying cause.
- Aspirin usually settles both pain and fever; indomethacin is particularly useful in preventing recurrence; a short course of steroids may be needed.
- Small effusions can be followed clinically and with the aid of two-dimensional echocardiograms.

Nonpharmacological treatment

- For tamponade, pericardial aspiration may be life-saving with large effusions.
- As much fluid as possible should be drained; blood-stained effusions usually signify malignancy, but all samples should be sent for cytology and bacteriology.
- Pericardiocentesis alone frequently results in the resolution of large effusions, but recurrence is common.
- Recurrent effusions may need balloon pericardotomy or surgical drainage.
- Chemotherapy can be started if malignant disease has been confirmed.

Treatment aims

To prevent adverse hemodynamic changes of tamponade.

To diagnose and treat underlying condition.

Prognosis

- Prognosis depends on the underlying condition: it is good for viral pericarditis but poor for malignant pericardial effusion.
- Patients with viral pericarditis usually recover completely in 1–2 weeks.
- Large idiopathic chronic pericardial effusion is well-tolerated for long periods in most patients, but severe tamponade can develop unexpectedly at any time.

Follow-up and management

- Regular echocardiographic follow-up is necessary for pericardial effusions.

General references

Clifford CP, Davies GJ: Tuberculous pericarditis with rapid progression to constriction. *BMJ* 1993, **307**:1052–1054.

Sagrista-Sauleda J, *et al.*: Long-term follow-up of idiopathic pericardial effusion. *N Engl J Med* 1999, **341**:2054–2059.

Ziskind AA, *et al.*: Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. *J Am Coll Cardiol* 1993, **21**:1–5.

Diagnosis

Definition [1]

• Personality disorders are dysfunctional patterns of thinking and behavior that reflect persistent ways of relating to self and others, which deviate markedly from the norm and are invariably accompanied by impairment of social role or major subjective distress.

•The specific personality disorders that appear in adolescence can be broadly categorized into three main areas:

Flamboyant: histrionic, emotionally unstable (borderline or impulsive), dissocial.

Eccentric: paranoid/schizoid.

Fearful: anancastic, anxious/avoidant, dependent.

• Others are acquired later in life and arise as a result of organic insult, psychiatric illness, or catastrophic stress.

Symptoms and signs

Suspicion, oversensitivity, querulousness, unforgiving: paranoid.

Emotional coldness, solitude, social insensitivity: schizoid.

Impulsiveness, emotional instability, poor self-control: emotionally unstable (impulsive or borderline).

Obsessions, perfectionism, rigidity, self-doubt: anancastic.

Social sensitivity, apprehension, feelings of social inferiority: anxious, avoidant.

Reliance on others, subordination of own needs, fear of abandonment: dependent.

Callousness, irresponsibility, blaming others, aggressiveness: dissocial.

Dramatics, suggestibility, seeking center stage, shallowness: histrionic.

• Patients often place high demands on the health care system because of somatization and demand for medication. Behaviors include frequent calls, emergency visits, and prolonged office visits. Health care providers are frequently frustrated and drained, especially if the personality disorder is undiagnosed.

Investigations

History: should be corroborated with other sources if possible (with patient's permission): personality characteristics of parents, early development, adverse life events and upbringing; school/social services (history of neglect, impoverishment, or abuse); legal sources (*e.g.,* probation office); spouse, cohabitee (partners may also have personality disorders); employer.

Standardized questionnaires: usually time-consuming but highly reliable; patients are asked tightly worded questions covering specific areas of personal and social function in order to avoid biased judgement on the part of the therapist; this is particularly important in the case of disorders with antisocial characteristics.

Munich Checklist for ICD-10: a good alternative [2].

EEG: finding may be abnormal in patients with dissocial disorder.

Complications

High suicide rate.

Self-harming behavior: may lead to frequent presentations in a wide variety of health care settings, *e.g.*, emergency departments, medical wards.

Alcohol addiction and drug abuse.

Harm to others: *e.g.*, violent assault or sexual abuse of children.

Differential diagnosis

Comorbidity with mental illness (AXIS I): cross-sectional studies show that ~40% of patients also manifest AXIS I disorders when they present in clinical settings.

Schizotypal disorder: frequently overlaps with borderline and schizoid disorders.

Prodromal or residual phase of schizophrenia.

Affective disorders: hypomania may mimic dissocial disorder; depression is frequent in patients suffering from borderline disorder.

Etiology

Genetic inheritance.

Abnormal developmental biology.

Failure to negotiate critical stages of emotional development.

Childhood trauma: sexual abuse is a more frequent feature in borderline disorders.

Social theories: abnormal parenting or lack of an appropriate role model.

Epidemiology

• Because sufferers avoid society, schizoid personality disorder appears to be rare .

• The prevalence in the general population is 2%–6%; in primary care settings, 15%–34%; in psychiatric outpatients, 20%–40%; in psychiatric inpatients, 40%–60%; in forensic settings, 50%–90%.

Treatment

Diet and lifestyle

• No special precautions are necessary.

Pharmacological treatment [3]

• All drugs must be used with caution because of the dangers of overdose and abuse.

• Neuroleptics, *e.g.*, thioridazine or haloperidol in low doses, can alleviate symptoms, *e.g.*, hostility, anger, suspiciousness, and depressed mood, in borderline or dissocial conditions.

• Monoamine oxidase inhibitors may be useful in borderline conditions.

• Long-term use of benzodiazepines must be avoided because of the probability of addiction; they may cause paradoxical disinhibition.

• Mood stabilizers (lithium and carbamazepine) are most useful if there is evidence of mood swings or family history of affective disorder.

Nonpharmacological treatment

Psychotherapy

• Interpretative psychotherapies for flamboyant disorders are effective in mild to moderate conditions.

Behavior or cognitive therapy

• This is being developed but is not widely available; it is similar to therapies used in the treatment of depression and anxiety.

• Effective in decreasing symptoms in milder cases in which somatization is a prominent feature [4].

Supportive therapy

• This includes social support and is most useful for patients with severe disruptive personality disorders.

• Patients are encouraged to find practical solutions to present problems, *e.g.*, relationship difficulties, accommodation, other personal needs.

Group therapy

• Group therapy may help patients with some forms of personality disorders.

• It includes the use of therapeutic communities.

Office management

• Frequent, brief, focused visits are the mainstay. Legitimization of symptoms, brief physical examination of symptomatic areas, and specific planning for next contact should be included.

• Setting limits on between-visit and within-visit behavior (*e.g.*, phone calls, referrals, medication use) is important to limiting burden on office staff.

• Long-term objectives include increased social functions, decreased use of emergency services, decreased use of medications, and avoidance of physician and staff burnout.

Treatment aims

To alleviate subjective distress and reduce impact of dysfunctional behavior.

Prognosis

• Prognosis is usually poor in severely affected patients, but most improve with age (4th or 5th decade); improvement is more noticeable for the flamboyant group.

• The outcome is invariably worse when comorbid mental illness is present.

• Good prognostic features include intelligence and the presence of positive adaptive traits, *e.g.*, candor and introspectiveness.

Follow-up and management

• No treatment has universally proven effectiveness; the most useful approach is based on long-term supportive contact and crisis intervention when needed.

• Patients tend to arouse strong feelings in therapists; staff working in crisis situations particularly need regular support.

Danger

• Most patients with personality disorders are no more dangerous than unaffected people.

• A few people with severe disorders, especially those with paranoid or dissocial traits, can exhibit considerable aggression toward others; safety and surveillance is paramount in such circumstances.

• In community settings, the police should be involved to make the situation safe.

• Admission to secure units or forensic facilities may be needed.

Key references

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2. Bronisch T, *et al.*: The Munich diagnostic checklist for the assessment of DSM–III-R personality disorders for use in routine clinical care and research. *Eur Arch Psychiatry Clin Neurosci* 1992, **242**:77–81.
3. Stein G: Drug treatment of personality disorders. *Br J Psychiatry* 1992, **166**:67–84.
4. Speckens AM, *et al.*: Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trail. *BMJ* 1995, **311**:1328–1332.

Diagnosis

Symptoms

Sore throat: with difficulty swallowing.
Concurrent coryza, laryngitis, productive cough: suggesting viral cause.
Malaise, fever, headache: common.

Signs

General

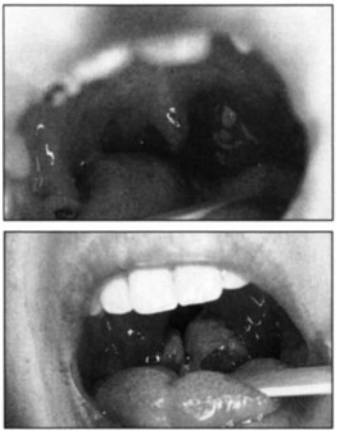
Injected mucous membranes of pharynx, tonsils, conjunctivae, and tympanic membranes.
Enlarged tonsils: sometimes with exudates.
Enlarged cervical lymph nodes.

Streptococcal infection

Grey exudates in tonsillar follicles.
Enlarged injected tonsillar and peritonsillar area.
Coated tongue with fetor.
Enlarged, tender cervical nodes.
Occasional meningismus.
Diffuse punctate erythema, flushed cheeks, circumoral pallor, reddened mucous membrane, white then red strawberry tongue: signs of scarlet fever.

Infectious mononucleosis

Prolonged fever: often for 10–14 days.
Nasal voice/"fish mouth" breathing.
Enlarged lymph nodes and splenomegaly.
Palatal petechiae and clean tongue.
Enlarged tonsils: sometimes almost meeting in middle, with confluent white exudates.
Faint maculopapular rash.



Streptococcal follicular tonsillar exudates (*top*) and confluent exudates (*bottom*) in infectious mononucleosis. (See Color Plates.)

Coxsackie A virus

5–10 small aphthoid ulcers: scattered over oral cavity.
Firm vesicular lesions: along sides of fingers and on feet (usually few).
Papular lesions: especially on feet and lower legs, occasionally up to buttocks.

Diphtheria

Toxic, listless, tachycardia due to myocarditis: fever usually low-grade or nonexistent.
Adherent whitish membrane: spreading from tonsils to oropharynx or oral cavity.
Enlarged anterior cervical lymph nodes: with surrounding edema.

Investigations

Throat swab: to check for streptococcal infection and diphtheria; usually not needed for viral infections. Rapid streptococcal test.
Differential leukocyte count: elevated neutrophil leukocytosis indicates streptococcal infection; elevated, many atypical mononuclear cells indicate infectious mononucleosis.
Serology: for Epstein–Barr virus, mycoplasma.

Complications

Peritonsillar abscess, reactive phenomena (rheumatic fever, glomerulonephritis, erythema nodosum, Henoch–Schönlein purpura): with streptococcal infection.
Respiratory obstruction, hepatitis, splenic rupture: with infectious mononucleosis.
Nerve palsies, myocarditis: with diphtheria.
Erythema multiforme: with *Mycoplasma pneumoniae* infection.

Differential diagnosis

- Differential diagnosis depends on the underlying cause.

Etiology [1]

- Causes include the following:

Pharyngitis with nonspecific features
Viral infection, especially adenoviruses, enteroviruses, influenza or parainfluenza virus, Epstein–Barr virus, coronavirus.
Beta-hemolytic *Streptococcus pyogenes* group A, C, or G.
M. pneumoniae, Corynebacterium diphtheriae, Neisseria gonorrhoeae.

Pharyngitis with clinically recognizable features
Streptococcus pyogenes infection: cause of follicular tonsillitis, scarlet fever.
Epstein–Barr virus infection: cause of infectious mononucleosis.
Coxsackievirus infection: cause of hand, foot, and mouth disease (A16), herp-angina (A).
C. diphtheriae infection: cause of diphtheria.

Epidemiology

- Very common disease of adults and children.
- Adenoviral infection is the most common viral type identified in children with respiratory illnesses, which are more prevalent in crowded conditions.
- Enteroviral infection usually occurs in late summer or early autumn, with one or two types dominating (out of >70).
- Some influenza virus activity is usual each winter, with some larger outbreaks.
- Epstein–Barr virus circulates throughout childhood but is usually only manifest symptomatically in teenagers and young adults.
- Streptococcal infection occurs in late winter and early spring, especially in school children.
- Very few cases of diphtheria occur in the United States each year.

Treatment

Diet and lifestyle

• Infants should be breast-fed and subsequently provided with adequate nutrition throughout childhood.

• Respiratory secretions must be disposed of hygienically.

Pharmacological treatment [2]

• Immunization should be given as nationally recommended: *e.g.*, against diphtheria, influenza A.

• Symptomatic treatment is indicated for presumed viral infections: *e.g.*, throat lozenges, acetaminophen.

Antibiotics

• Penicillins are effective against streptococcal and diphtherial infections [3,4].

Standard dosage	Penicillin G, 1.2 MU i.m. Phenoxymethylpenicillin, 500 mg orally every 6 hours.
Contraindications	Hypersensitivity.
Special points	Erythromycin, 250 mg every 6 hours, or new macrolides are other options.
Main drug interactions	None.
Main side effects	Sensitivity reactions, diarrhea.

Antitoxin

• Antitoxin should be given immediately on clinical suspicion of diphtheria.

Standard dosage	Antitoxin 20 000–100 000 units i.v. (depending on disease severity).
Contraindications	Hypersensitivity (epinephrine should be available).
Special points	Test dose is needed before full dose because of equine origin of antitoxin.
Main drug interactions	None.
Main side effects	Sensitivity reactions, including serum sickness.

Alternative medicine

Recommended use: Purple coneflower (*Echinacea* spp.).

Common use: hyssop (*Hyssopus officinalis*); sage (*Salvia officinalis*); Lady's mantle (*Alchemilla vulgaris*); pokeroot (*Phytolacca americana*); coltsfoot (*Tussilago farfara*).

Caution: none.

Treatment aims

To provide symptomatic relief.
To reduce infectivity.
To prevent rheumatic fever (in streptococcal infections).
To neutralize circulating toxins of diphtheria promptly.

Other treatments

Drainage of peritonsillar abscess, indicated by marked inferior and posterior displacement of tonsil.
Tracheostomy for respiratory obstruction.
Tonsillectomy in children with recurrent tonsillitis that disrupts schooling.

Prognosis

• Full rapid recovery is usual.
• Occasionally, patients suffer from post-viral fatigue, especially after influenza, Epstein–Barr, or enteroviral infections.
• Mortality from diphtheria is 5%–10%; survivors usually recover completely.

Follow-up and management

• Patients who have apparently recovered from streptococcal tonsillitis may continue to have enlarged and tender cervical nodes that subsequently spread infection as cellulitis or septicemia.
• Patients with diphtheria should be followed up after 2–6 weeks for late nerve palsies and myocarditis.

Notification

• Diphtheria and scarlet fever are legally notifiable diseases in the United States.

Key references

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Pilonidal disease

Diagnosis

Symptoms

Palpable swelling in the soft tissue overlying the sacrococcygeal junction.

Pain.

Drainage.

Fevers, symptoms of systemic infection: unusual.

Signs

Midline localized inflammation, most commonly in the region internatal or gluteal cleft.

Possible abscess formation.

Sinus tract: directed cephalad.

Absence of perianal inflammation or other signs of a perianal fistula.

Investigations

Careful digital rectal examination and, if necessary, anoscopy: to exclude perianal inflammation or communication with the anorectum.

Complications

Chronic abscess.

Persistent or recurrent cellulitis.

Sepsis and/or osteomyelitis: rare.

Squamous cell carcinoma: rare.

Differential diagnosis

Perianal fistula/abscess.
Hidradenitis suppurativa.
Carbuncle or furuncle.
Osteomyelitis.

Etiology

Acquired process from torsion on hair growing in the gluteal cleft resulting in folliculitis and sinus formation.

- Risk factors include family predisposition, prolonged sitting, obesity.

Epidemiology

- Incidence is 26 cases per 100 000.
- It is most common in the third decade and rarely occurs preadolescence.
- Male:female ratio is 3:1.

Treatment

Diet and lifestyle

• Patients with recurrent problems benefit from shaving the hairs in the sacrococcygeal region.

Pharmacological treatment

Cellulitis should be treated with a course of antibiotics that will cover *Staphylococcus* and *Bacteroides* spp. (e.g., Augmentin).

Standard dosage Augmentin, 500 mg every 8 hours for 10 days.

Contraindications Penicillin allergy.

Main side effects Antibiotic-related diarrhea.

Treatment aims

To relieve pain.

To control infection.

To prevent recurrence.

Other treatments

• Patients with tender, localized nodules are best treated by surgical drainage rather than antibiotics.

• Definitive surgical management with resection of midline holes and pits that sustain abscesses is necessary in patients with recurrent disease.

• Sclerosing therapy is occasionally used to manage recurrent disease.

Prognosis

• 80% of patients are successfully treated long-term with simple drainage procedures.

Follow-up and management

• As noted earlier, removal of hair by shaving the sacrococcygeal region of the natal cleft probably reduces the recurrence of the disease.

General references

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Platelet disorders

Diagnosis

Symptoms

• Platelet disorders may be manifest by bleeding or discovered incidentally in an otherwise asymptomatic patient.

Bruising.

Bleeding: usually mucosal, *e.g.*, gingival, nasal, gastrointestinal, menorrhagic; occasionally retinal (loss of vision) or intracranial (headache); after surgical procedures.

Deafness: in some familial disorders.

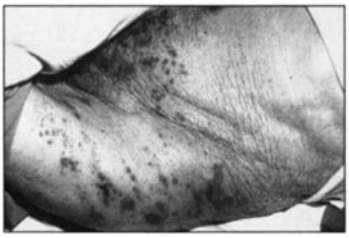
Signs

Petechiae, purpura, bruises.

Retinal hemorrhages.

Thrombosis and skin microinfarcts: in thrombotic thrombocytopenic purpura.

Capillary bleeding.



Purpura due to thrombocytopenia. (*See* Color Plate.)

Investigations

• Initial investigations are used to identify primary platelet disorder and to exclude von Willebrand's disease in patients with a strong family history and lifelong bleeding disorder.

Complete blood count: platelet count and mean platelet volume, to exclude other hematological disease and pseudothrombocytopenia due to clumping or EDTA (ethylene- diaminetetra-acetic acid)-induced aggregation.

Microscopic examination of film: for platelet morphology, to detect erythrocyte or leukocyte abnormality.

Coagulation screening: to exclude primary coagulopathy.

Biochemistry profiles: to identify renal or hepatic disease.

Platelet function tests: bleeding time, if prolonged, suggests platelet function disorder or von Willebrand's disease (drugs that affect platelet function, *e.g.*, aspirin, should be avoided for 10 days before testing); spontaneous in vitro aggregation and response to ADP (adenosine diphosphate), collagen, and ristocetin should be recorded; if abnormal, response to other agonists (*e.g.*, epinephrine, thrombin, arachidonate) should be assessed; release reaction of radiolabeled 5-HT (5-hydroxytryptamine); measurement of platelet adenine nucleotides; hereditary and some acquired platelet disorders have characteristic aggregation responses.

Bone-marrow aspiration and biopsy: in most patients with thrombocytopenia, to assess number and structure of megakaryocytes and bone-marrow function.

Platelet serology: in posttransfusion purpura and in neonates with alloimmune thrombocytopenia, to identify specific antiplatelet antigen antibodies.

Platelet-associated immunoglobulin measurement: nonspecific, often increases in immune thrombocytopenias.

Flow cytometry: to quantify platelet membrane glycoproteins, using monoclonal antibodies to detect hereditary disorders.

Complications

Iron-deficiency anemia: caused by menorrhagia or recurrent epistaxis or gastrointestinal bleeding.

Neurological impairment or death: caused by intracranial bleeding.

Differential diagnosis

Bleeding disorders

Von Willebrand's disease.
Fibrinogen disorders.

Purpura

Vasculitis: *e.g.*, Henoch-Schönlein syndrome.
Amyloid.
Senile purpura.
Scurvy.
Steroid treatment.
Collagen disorders (*e.g.*, Ehlers–Danlos syndrome).
Hereditary hemorrhagic telangiectasia (does not cause purpura but can lead to low platelet count in extreme forms).

Etiology [1,2]

Decreased production

Bone-marrow failure: leukemia, metastatic tumor, idiopathic aplasia, infiltration, abnormal production, myelodysplasia, aplastic anemia, drugs (predictable, *e.g.*, cytotoxic drugs, or idiosyncratic reactions).

Increased consumption

Immune: autoimmune (idiopathic, post-viral, HIV, associated with other autoimmune disorders), alloimmune against platelet-specific antigens, *e.g.*, HPA-1.
Drugs: *e.g.*, quinine, heparin, sulfonamides, rifampin.
Coagulopathy: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura.
Hypersplenism and splenomegaly.

Hereditary

Platelet membrane glycoprotein abnormalities, *e.g.*, Bernard-Soulier and Glanzmann's diseases.
Platelet storage pool abnormalities.
Other abnormalities, *e.g.*, May–Hegglin anomaly.

Acquired

Platelet storage pool defects: *e.g.*, aspirin, uremia, ethanol, cirrhosis, myeloproliferative disorders.

Epidemiology

• Acquired disorders of platelet function are common and are associated with disorders such as chronic renal failure or the ingestion of aspirin.

• Chronic idiopathic thrombocytopenic purpura is relatively common (one group suggests that 0.18% of patients admitted to hospital in a 10-year period had the disease).

Treatment

Diet and lifestyle

• Patients should avoid trauma and contact sports.

Pharmacological treatment

For immune thrombocytopenia [3,4]

• In children, the onset is usually acute and often follows a viral infection; spontaneous recovery is common, and treatment is given to those with severe or life-threatening bleeding to elevate the platelet count. In adults, the onset is more insidious, and the condition almost never remits spontaneously.

Standard dosage — *Children:* immunoglobulin, 0.4 g/kg i.v.daily (in 4–6 hours) for 5 days (sometimes 1.0 g/kg daily for 2 days); or prednisone, 1 mg/kg.
Adults: prednisone, 1 mg/kg daily initially until maximum response, then tapered off.

Contraindications — *Prednisone:* active infection, diabetes mellitus.

Main drug interactions — *See manufacturer's current prescribing information.*

Main side effects — *Immunoglobulin:* headache, hypertension, tachycardia.
Prednisone: hypertension, diabetes mellitus, osteoporosis.

• Adults who do not respond or who relapse when steroids are reduced should be considered for splenectomy.

• Other treatments for adults in whom steroids or splenectomy fails include i.v. immunoglobulin, azathioprine, vinca alkaloids, danazol, high-dose dexamethasone, or vitamin C.

For platelet functional defects [5]

• Bleeding tendency is often mild, and specific treatment is needed for major hemorrhage or to cover surgical procedures. Antifibrinolytic agents may be helpful to control minor bleeding; antiovulatory treatment may be needed for menorrhagia.

Standard dosage — One donor platelet pack/10 kg body weight or one platelet pheresis pack should raise the platelet count.
DDAVP, 0.4 μg/kg i.v. in 100 mL 0.9% saline solution in 15–20 minutes.
Tranexamic acid, 0.5–1.0 g 3 times daily orally or i.v.
Aminocaproic acid, 2–4 g 4 times daily orally.

Contraindications — *DDAVP:* coronary artery disease.
Tranexamic acid and aminocaproic acid: history of thromboembolism and hematuria.

Special points — *DDAVP:* ineffective in Glanzmann's thrombasthenia.

Main drug interactions — *See manufacturer's current prescribing information.*

Main side effects — *Platelet transfusion:* allergic reactions, HLA or alloimmunization in multitransfused patients; hepatitis B (rare) or C virus transmission.
DDAVP: nausea, tremor, vomiting, angina, myocardial infarction.
Tranexamic acid: nausea, vomiting, diarrhea.

For bone-marrow disorders

• The risk of spontaneous hemorrhage increases when the platelet count is $<10 \times 10^9$/L. Prophylactic platelet transfusions are given to maintain the count above this level during the treatment of acute leukemia or aplastic anemia or during bone-marrow transplantation.

• In chronic thrombocytopenia due to bone-marrow failure, platelet transfusions are given for symptomatic bleeding.

For thrombotic thrombocytopenic purpura [6]

Supportive therapy of medical complications, *e.g.*, hemodialysis. Plasma exchange with fresh frozen plasma replacement (1.5 times plasma volume) for 7 days. Additional treatments include aspirin, dipyridamole, methylprednisone, and vincristine.

For alloimmune thrombocytopenia, neonatal and posttransfusion

Antigen-negative platelet transfusion, i.v. immunoglobulin, prednisone, or plasma exchange.

Treatment aims

To cure or alleviate symptoms.

Other treatments

• Splenectomy is indicated for immune thrombocytopenia in those >6 y).

• Vaccination by Pneumovax and against *H. influenzae* type b and *N. meningitidis* serogroups A and C should be given 1–2 weeks before surgery.

Lifelong antipneumococcal prophylaxis is recommended for patients who have had splenectomy.

Prognosis

• Up to 90% of children with idiopathic thrombocytopenic purpura remit spontaneously, with 50% recovering in 1 month.

• 80% of adults with idiopathic thrombocytopenic purpura remit after treatment by steroids alone or after splenectomy.

• In patients with acquired platelet function defects, prognosis related to underlying disease.

• Mortality in patients with untreated thrombotic thrombocytopenic purpura is up to 90%; 60%–80% respond to treatment.

• Alloimmune thrombocytopenias are self-limiting but potentially fatal.

Follow-up and management

• Frequency depends on the clinical severity and stability of underlying disorder.

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Pleural effusion

Diagnosis

Symptoms

• Patients are often asymptomatic if the effusion is small.

Breathlessness.

Chest pain: increased on deep inspiration or movement.

Positional discomfort or pain: with large effusions, causing mediastinal shift.

Symptoms of underlying disease.

Fever.

Signs

• Signs are clinically detectable only if the volume is ≥300 mL; loculated effusion may be very difficult to detect.

Decreased movement of chest wall on affected side.

Dullness to percussion.

Absent breath sounds in area of dullness.

Occasional bronchial breathing at upper margin of area of dullness.

Displaced trachea: large effusions only.

Decreased tactile tremitus.

Investigations [1,2]

Chest radiography: to assess extent of effusion and free-flowing character.

Ultrasonography: if doubt about nature of shadowing and to define loculated area for aspiration.

Aspiration: for cytology, Gram stain and Ziehl-Neelsen stain for acid-fast bacilli, culture, protein content, lactate dehydrogenase (LDH), cell count and differential, pH, glucose.

• Comparison of pleural protein content and LDH to plasma protein and LDH is essential to distinguish between transudative and exudative effusions [3].

Pleural biopsy: in experienced hands, much more reliable for diagnosis of tuberculosis and malignancy than simple aspiration.

Repeat radiography: after drainage of effusion, to visualize underlying lung.

Thoracoscopy: if doubt remains, to obtain better samples for histology.

CT: for visualizing loculated effusions and pleural and parenchymal disease.

Complications

Constrictive fibrosis of pleura and restricted lung function: caused by empyema and postpneumonic effusions.

Iatrogenic secondary infection.

Iatrogenic pneumothorax.

Unilateral pulmonary edema: after injudiciously rapid drainage (rare).

Hemorrhage: damage to intercostal vessels, especially after pleural biopsy.

Differential diagnosis

Infections: postpneumonic, tuberculosis.

Inflammation: pancreatitis, rheumatoid arthritis, SLE, polyarteritis nodosa.

Primary malignancy: mesothelioma.

Secondary malignancy: bronchogenic carcinoma, metastatic spread (especially breast, stomach, pancreas), lymphoma.

Infarction secondary to pulmonary embolism.

Etiology

Exudates

Unknown in ~20%, despite extensive investigation.

Infections: viral pleurisy, bacterial pneumonia, tuberculosis, empyema.

Secondary malignancy or secondary cancer (e.g., lung, breast, stomach), leukemia or lymphoma.

Vascular: pulmonary infarction, pulmonary embolism.

Collagen disorders: rheumatoid arthritis.

Primary pleural malignancy (mesothelioma).

Uremia, chylothorax.

Transudates

Congestive heart failure, hypoalbuminemia (nephrotic syndrome and hepatic cirrhosis), constrictive pericarditis, pulmonary embolism.

Peritoneal dialysis.

Epidemiology

• Pleural effusion is frequently found with lung cancer and pneumonia.

• Tuberculosis is declining in importance but remains one of the most common causes of pleural effusion worldwide.

• Mesothelioma is rare. It is associated with asbestos exposure.

Treatment

Diet and lifestyle

• No special precautions are necessary.

Pharmacological treatment

Principles

• The principal aim is to treat any underlying cause and to treat the local problem by drainage.

• For transudates, the underlying disease must be treated.

• For infective causes (empyema, pneumonia), systemic antibiotics are indicated and intercostal drainage is essential; surgical drainage and decortication of pleura can be done if thick pleural rind develops.

• For tuberculosis, standard oral antituberculosis chemotherapy is indicated. The effusion should be aspirated to dryness. Tube drainage and surgery should be avoided if possible. *See* Tuberculosis, pulmonary *for details.*

• For malignant effusions, pleural effusion indicates inoperability; treatment is guided by symptoms. Intermittent aspiration is usually helpful. Tube drainage is the best method of preventing recurrence and achieving pleurodesis. In mesothelioma, tube drainage is best avoided if possible because of the risk of seeding tube tract [4,5].

• For noninfective nonmalignant causes, the effusion should be drained to dryness and followed with repeated chest radiographs.

• Pulmonary infarcts usually resolve without needing drainage, but formal anticoagulation with warfarin is usually appropriate (*see* Pulmonary embolism *for details*).

Chemical pleurodesis [5,6]

• Chemical pleurodesis is best done by specialists, who can consider the advantages and disadvantages in each individual case. It is usually reserved for malignant pleural effusions.

• Although many different agents ranging from antibiotics to antiseptics to antineoplastics to talc have been advocated, none is ideal.

• The agent most commonly used is talc. It may be insufflated via thoracoscopy or instilled as a slurry.

• Other approaches include the following:

Standard dosage	Doxycycline, 500 mg, or minocycline, 300 mg in 50 mL saline, after pleural fluid has been drained. A second dose may be given after 72 hours. Bleomycin, 60 U is an alternative for malignant effusions.
Contraindications	Transudate, bronchopleural fistulas, infection.
Main drug interactions	None.
Main side effects	Local pain, transient fever, hypersensitivity reaction.

Treatment aims

To achieve resolution of pleural effusion without residual fibrosis or functional deficit.

Prognosis

• Prognosis varies widely according to the underlying cause.

• If cleared by drainage, most bacterial effusions resolve, leaving some pleural scarring, which may need surgery if severe.

• Malignant effusions have poor prognosis, and treatment is mainly palliative, guided by symptoms.

Follow-up and management

• Serial chest radiographs should be taken, usually at 4–6-week intervals to assess recurrence.

• Lung function tests are needed to assess residual restrictive deficit if radiographic changes persist.

Key references

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Pneumocystis carinii pneumonia in AIDS

Diagnosis

Symptoms

Fever, fatigue, weight loss: for weeks before respiratory symptoms develop.

Nonproductive cough, shortness of breath: initially on exertion, then at rest with disease progression.

• The absence of respiratory symptoms does not exclude *Pneumocystis carinii* pneumonia.

Signs

Tachypnea, rales without consolidation: revealed by auscultation, but often no pulmonary abnormalities.

Investigations

• *P. carinii* pneumonia occurs in HIV-infected individuals who have a CD4 lymphocyte count $<200 \times 10^6$/L.

Complete blood count: to exclude anemia.

Plain chest radiography: may show diffuse interstitial infiltration; various other appearances, including lobar infiltrate cavity or pneumothorax, occur. Chest radiograph may be normal early in the course of the infection.

Arterial oxygen tension measurement: hypoxia commonly occurs.

Exercise oximetry: a useful noninvasive test.

Sputum analysis: obviates need for routine bronchoscopy if laboratory is experienced; sputum induced by inhaled nebulized hypertonic saline solution; samples stained by Grocott or immunofluorescent stains.

Fiberoptic bronchoscopy: reserved for patients whose induced sputum test results are not diagnostic.

Complications

Pneumothorax.

Restrictive lung disease.

Extrapulmonic *P. carinii* infection.

Acute respiratory distress syndrome.

Differential diagnosis

Bacterial pneumonia.
Pulmonary Kaposi's sarcoma.
Pulmonary tuberculosis.
Toxoplasmosis.
Pulmonary lymphoma.
Asthma.
Cytomegalovirus pneumonitis.
Lipid interstitial pneumonitis.
Histoplasmosis.
Aspergillosis.

Etiology

• The pneumonia is caused by infection by *P. carinii*.

• Acquisition may be common early in life (and controlled by the immune system) or occur shortly before the disease develops.

Epidemiology

• Most children have serological evidence of previous *P. carinii* infection by the age of 4 years; the disease was first recognized because of epidemics in orphanages after World War II.

• The disease is the most common AIDS opportunistic infection in people with HIV-induced immunosuppression, with no difference between genders or among races, although it occurs significantly less often in many developing countries.

Treatment

Diet and lifestyle

Not applicable.

Pharmacological treatment

Treatment of the disease

- The most effective agent is trimethoprim-sulfamethoxazole (TMP-SMX); in less severely ill patients, oral treatment may be used.
- Unfortunately, many patients are unable to complete a treatment course because of allergic or toxic side effects.
- Alternative treatment in bactrim-intolerant individuals with mild to moderate disease includes clindamycin and primaquine, or trimethoprim and dapsone or atovoguore. For patients with severe infection, the alternates to bactrim are pentamidine and trimetrexate.
- Corticosteroids have been shown to reduce mortality and the risk of respiratory failure in patients presenting with partial arterial oxygen pressure <70 mmHg.

Standard dosage	TMP-SMX, 15 mg/kg daily, given in 3 divided doses.
Contraindications	Hypersensitivity.
Special points	Full blood count, U&E monitoring, and liver function tests must be done.
Main drug interactions	None.
Main side effects	Nausea and vomiting (antiemetic can be given), skin rash, leukopenia, thrombocytopenia, raised liver function tests.

Prophylaxis

- Primary prophylaxis is recommended in patients with clinical evidence of immunosuppression (*e.g.*, buccal candidiasis) or other opportunistic infections or laboratory evidence (CD4 count $<200 \times 10^6$/L).
- Secondary prophylaxis should be offered to patients who have had previous episodes of *P. carinii* pneumonia.

Standard dosage	TMP-SMX, 1 tablet daily. Alternatively, dapsone, 100 mg daily, or pentamidine, 300 mg inhaled every month.
Contraindications	Allergy to sulfonamides or trimethoprim.
Special points	TMP-SMX may also reduce the incidence of subsequent toxoplasmosis and bacterial infection.
Main drug interactions	None.
Main side effects	Skin rash, nausea and vomiting, leukopenia, thrombocytopenia, raised liver function tests.

Treatment aims

To treat pneumonia.

To suppress future infection.

Prognosis

- Mortality for the first episode of *P. carinii* pneumonia is <10% but is higher for subsequent attacks.

Follow-up and management

- Complete blood count should be done after treatment because anemia is common.
- Patients should be followed up at least monthly.

General references

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Santamauro JT, Stover DE: *Pneumocystis carinii* pneumonia. *Med Clin North Am* **81**:299–318.

Pneumonia

Diagnosis

Symptoms

Common

• Onset may be abrupt or over days.

Cough: with sputum, which may be purulent, in two-thirds of patients.

Fever: possibly with rigors and diaphoresis.

Pleuritic chest pain: occasionally.

Dyspnea.

Less common

Hemoptysis, vomiting, diarrhea, myalgia.

Mental confusion: especially in patients with severe pneumonia and in elderly patients.

Signs

Fever.

Mental confusion, cyanosis, hypotension: suggesting severe illness.

Increased respiratory rate: suggesting severe illness.

Dullness on percussion.

Increased vocal fremitus.

Crackles.

Bronchial breathing: egobronchophony and whispering pectoriloquy; in one-third of patients.

Investigations [1]

To confirm diagnosis

Chest radiography: shows consolidation or infiltrates.

To assess severity

Arterial blood gas analysis: low partial oxygen pressure, raised partial carbon dioxide pressure, low pH.

Complete blood count: leukocytosis with left shift (leukocyte count <4 or >20 × 10^9/L indicates high risk).

To assess cause

Blood culture: for bacteremia.

Sputum Gram stain and culture: to exclude *Legionella* and *Pneumocystis* spp. and mycobacteria.

Pleural-fluid Gram stain and culture: if fluid present.

Serology: acute and convalescent sera for antibodies to viruses, chlamydia, mycoplasma, *Coxiella* spp., and legionella.

Bronchoscopy: often needed in immunocompromised patients but rarely in others.

Complications

Empyema, lung abscess, pulmonary embolus, acute respiratory distress syndrome.

Acute renal failure, hemolysis.

Sepsis.

Death: especially in the elderly, often despite appropriate therapy.

Differential diagnosis

Pulmonary edema.

Exacerbation of chronic bronchitis.

Pulmonary embolus.

Lung cancer.

Etiology [2,3]

• Pneumococcal infection is the cause of 50%–80% of community-acquired pneumonias.

• Gram-negative organisms (*e.g.*, *Escherichia coli* and *Pseudomonas* spp.) are the cause of 50% or more of nosocomial pneumonias.

• Anaerobic bacteria (*e.g.*, bacteroides) are important in aspiration pneumonia.

• Immunocompromised patients may be infected by a huge range of microorganisms, *e.g.*, unusual bacteria and fungi, many of which would not cause infection in immunocompetent patients.

Epidemiology [3]

• Pneumonia occurs at all ages but is most frequent in very young and very old patients.

• Primary care physicians see on average 10 cases annually.

• One patient in every five seen needs hospital admission.

• Most cases occur in the winter months.

• Mycoplasma infection affects mainly teenagers and young adults.

• Legionella infection may occur in epidemics related to water systems in buildings.

Classification

Community-acquired pneumonia.

Nosocomial pneumonia.

Aspiration pneumonia: caused by inhalation of oropharyngeal secretions, during vomiting, or when consciousness is depressed.

Immunocompromised pneumonia: *e.g.*, with HIV infection, organ transplantation, cytotoxic chemotherapy.

Treatment

Diet and lifestyle

• Smoking and smoking-related diseases are a major risk factor for pneumonia; smoking education is therefore important.

Pharmacological treatment [4,5]

General guidelines

Oxygen: to maintain partial oxygen pressure in arterial blood >60 mm Hg; may cause hypercapnia in patients with chronic obstructive pulmonary disease, so arterial blood gases should be monitored.

Oral or parenteral fluids: to correct dehydration.

Nonsedative analgesia: for pleuritic chest pain.

Physical therapy: especially if large sputum volumes are difficult to expectorate.

Intensive care, including assisted ventilation: valuable for patients in whom respiratory failure worsens despite treatment.

Antibiotics [7]

• Initial treatment must be empirical; this can be modified later if indicated by microbiological results.

• Oral antibiotics are appropriate in mild infection, parenteral if infection is severe or accompanied by vomiting.

• Treatment should be for at least 7 days; severely ill patients need treatment for up to 3 weeks.

For mild community-acquired disease: azithromycin, penicillin, cephalosporin, or erythromycin.

For severe community-acquired disease: 2nd- or 3rd-generation cephalosporin (*e.g.*, cefuroxime), possibly with erythromycin.

For nosocomial infection: 2nd- or 3rd-generation cephalosporin, possibly with aminoglycoside; usually requires 2–3 weeks of therapy.

For aspiration: amoxicillin-clavulanate or clindamycin.

For immunocompromised disease: individually determined by causative pathogen.

Standard dosage	Amoxicillin, 500 mg 3 times daily. Erythromycin, 500 mg 4 times daily. Cefuroxime, 750 mg 3 times daily. Aminoglycoside guided by blood level. Clindamycin, 300 mg 3 times daily.
Contraindications	Hypersensitivity.
Main drug interactions	Warfarin.
Main side effects	Diarrhea.

Prophylaxis

Annual influenza vaccination: for patients >65 years of age or those with chronic heart or lung disease, renal failure, or diabetes mellitus and for immunosuppressed patients.

Pneumococcal vaccination: for patients who are >65 years of age; asplenic; or have sickle cell disease, chronic renal failure, or chronic lung, heart, or liver disease; and those with diabetes mellitus or who are immunocompromised.

Criteria for hospitalization: age >65 years, co-existing illnesses (*e.g.*, diabetes, chronic obstructive pulmonary disease), tachypnea, tachycardia, hypotension, signs of sepsis, leukopenia, or severe leukocytosis.

Treatment aims

To improve oxygenation.
To achieve rapid resolution of pneumonia and return to normal activities.
To prevent death or sepsis.
To relieve symptoms.

Prognosis [6]

• Pyrexia usually settles within 48 hours of starting treatment.
• Lethargy after pneumonia often lasts weeks or months.
• Radiographic shadowing is slow to clear and lags behind clinical recovery.
• Death is unusual in patients managed at home.
• 5%–10% of patients admitted to hospital die.
• Up to 50% reaching intensive care die.
• The mortality in nosocomial pneumonia is up to 30% and may be higher in immunocompromised patients.

Follow-up and management

• Patients should be seen 6 weeks after presentation, and chest radiography repeated to confirm recovery and exclude underlying lung disease, especially lung cancer.

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Polycystic ovarian syndrome

Diagnosis

Symptoms

Oligomenorrhea or amenorrhea with sometimes heavy menses: endometrium remains estrogenized, in contrast with other causes or anovulation.

Infertility: due to anovulation.

Mild androgenism: hirsutism, acne, seborrhea [1].

Severe virilization (rare): alopecia, voice change, clitoromegaly.

Signs

• The signs associated with polycystic ovarian syndrome are extremely variable; in most women, the endocrine disturbance is subtle and the disorder has no outward signs.

Obesity.

Central adiposity.

Mild hypertension.

Hirsutism: documented by photography or Ferriman–Gallway score [1].

Acanthosis nigricans: feature of severe insulin resistance.

• Abdominal and pelvic examinations are rarely helpful but should be done to exclude ovarian masses.

Investigations [2,3]

• The aims are to make a positive diagnosis, to exclude other causes of anovulation, infertility, recurrent miscarriage and virilization as appropriate, and to screen for insulin resistance or frank diabetes mellitus (type 2).

• Diagnosis of polycystic ovarian syndrome should incorporate both an endocrine and a morphological assessment.

For the disorder

Chronic anovulation, hyperandrogenism: diagnostic criteria.

• The presence or absence of ovarian cysts is an unreliable finding, and not a diagnostic criterion.

To rule out other causes of amenorrhea

Pelvic examination.

Ultrasonography: to examine endometrium, possibly with endometrial biopsy (menstrual disorder); to diagnose ovarian tumors (virilization).

Serum testosterone measurement: tumor more likely if concentrations are markedly elevated.

For cardiovascular risk factors

Blood pressure measurement.

Evidence of insulin resistance or frank diabetes.

Serum lipid measurements.

Complications

Endometrial cancer: despite anovulation, ovaries continue to secrete estradiol.

Diabetes mellitus, myocardial infarction, stroke: related to insulin resistance [4].

Recurrent miscarriages: probably due to elevated androgen levels.

Differential diagnosis

Classic polycystic ovarian syndrome.
Hypothyroidism.
Cushing's syndrome.
Acromegaly.
Androgen-secreting tumor.
Estrogenized amenorrhea.
Granulosa cell tumor.

Etiology [3]

• Excess androgen production is of unclear etiology, often combined with insulin resistance.

Epidemiology [3]

• 10%–20% of apparently normal women are found to have polycystic ovaries on ultrasonography.
• 1% of young women (aged 15–40 years) have clinically evident disease.
• Family studies show the prevalence of polycystic ovaries to be high among asymptomatic close relatives (80%).
• The disease is a factor in ~10% of couples with infertility.

Treatment

Diet and lifestyle

• In view of the increased risk of cardiovascular disease, advice should be given about diet, smoking, lipid management, and exercise.

• A calorie-restricted diet may help by decreasing insulin resistance.

• Women with oligo- or amenorrhea not wishing to conceive should be warned of the small risk of conception.

Pharmacological treatment [3,5]

• Pregnancy must be ruled out before treatment begins.

• Polycystic ovarian syndrome is a diagnosis of exclusion, and other causes of amenorrhea must be investigated and ruled out.

For menstrual disorder

Combined oral contraceptive to improve regularity or reduce flow.

Cyclical progesterone or combined oral contraceptive to prevent endometrial neoplasia in women with oligo- or amenorrhea.

For anovulatory infertility

• Treatment should be carried out in conjunction with an appropriate specialist.

Antiestrogen treatment (clomiphene): acts through the hypothalamus.

Exogenous gonadotropin treatment: involves direct ovarian stimulation with human menopausal gonadotropin (hMG) or human follicle-stimulating hormone (hFSH), with human chorionic gonadotropin (hCG) to trigger ovulation.

Typical dosages	*Antiestrogen:* clomiphene, 100 mg orally daily on days 2–6 of cycle for up to 3 cycles. *Exogenous gonadotropin:* hMG or hFSH, 75 U daily.
Contraindications	Pregnancy, hormone-dependent tumors, undiagnosed abnormal menstruation.
Special points	*Antiestrogen:* near-normal conception rates expected; low risk of high-order multiple pregnancy (8% twin rate) and ovarian hyperstimulation; minimal monitoring needed (midluteal serum progesterone measurement). *Gonadotropin:* risk of multiple pregnancy and ovarian hyperstimulation; detailed monitoring mandatory (serial follicle scanning and estradiol measurement).
Main drug interactions	None.
Main side effects	*Antiestrogen:* hot flushes, mild abdominal discomfort, visual disturbance (rare). *Gonadotropin:* nausea, abdominal discomfort, allergy.

For virilization

Combined oral contraceptive: usual precautions for oral contraceptive use.

Flutamide or spironolactone: both are antiandrogens and may feminize a developing male fetus; therefore, contraception is of critical importance.

Special considerations

• Insulin-sparing agents such as metformin and thiozalidmediones (rosiglitazone and piaglitazone) are being evalutated as treatments for polycystic ovarian syndrome.

Treatment aims

To prevent long-term health risks, particularly those related to diabetes.

To alleviate symptoms.

To restore fertility.

Other treatments

Shaving, bleaching, electrolysis: for hirsutism.

Laparoscopic ovarian surgery: electrodiathermy or laser drilling; 80% ovulation rate; near-normal conception rate; normal twin rate and low miscarriage rate; effect lasts ~9 months on average.

Prognosis

• Acne and seborrhea respond within a few weeks, but the duration of the hair cycle means that improvement in hair growth may take many months.

• Symptoms generally return quickly after withdrawal of treatment.

Follow-up and management

• Follow up varies according to the disorder.

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Polymyalgia rheumatica & giant-cell arteritis

Diagnosis

Symptoms

Polymyalgia rheumatica

Pain and stiffness: bilateral and symmetrical, affecting neck, shoulder, and pelvic girdles; stiffness usually predominant, particularly severe after rest, and may prevent patient getting out of bed [1].

Malaise.

Depression.

Giant-cell arteritis

Headache: in two-thirds or more of patients; severe pain, usually localized in the temple but may be occipital or be less defined and precipitated by brushing the hair [2,3].

Pain on chewing: due to claudication of muscles of mastication, in up to two-thirds of patients.

Visual disturbances: in 25%; visual loss evident in <10%.

Malaise.

Depression.

Scalp tenderness.

Signs

Polymyalgia rheumatica

Unimpaired muscle strength: although pain makes interpretation of muscle testing difficult.

Tenderness of involved structures: with restriction of shoulder movement, if diagnosis delayed [1].

Peripheral synovitis: uncommon and transient.

Giant-cell arteritis

Scalp tenderness: particularly around temporal and occipital arteries; may disturb sleep [2].

Thickened, tender, and nodular arteries: with absent or reduced pulsation.

Partial or complete visual loss: due to anterior ischemic optic neuropathy [2,3].

Investigations

Baseline clinical investigations

• These are used to make the diagnosis and exclude other diagnoses.

ESR measurement: rate usually greatly raised, but can be normal [4].

Acute-phase protein (*e.g.*, CRP) measurement: concentration usually raised.

Complete blood count.

Biochemical profile.

Rheumatoid factor test.

Serum protein electrophoresis.

Thyroid function test.

Chest radiography.

Specific investigations

Temporal artery biopsy: for suspected giant-cell arteritis, not for polymyalgia rheumatica; findings can be focal, may be normal [2].

Segmental: skip areas.

Complications

Visual loss: in up to 10% of patients, permanent blindness in giant-cell arteritis [5]; usually not reversible.

Differential diagnosis

Neoplastic disease.

Joint disease: osteoarthritis (particularly of cervical spine), rheumatoid arthritis, connective tissue disease.

Multiple myeloma.

Leukemia.

Lymphoma.

Muscle disease: polymyositis, myopathy.

Infections: *e.g.*, bacterial endocarditis.

Bone disease: particularly osteomyelitis.

Hypothyroidism.

Parkinsonism.

Depression.

Etiology

• A distinct prodromal event is often noted, resembling influenza, although viral studies are negative.

• HLA-DR4 is increased in both polymyalgia rheumatica and giant-cell arteritis.

• Lymphocytes in arteritic lesions express the T-cell phenotype, and the $CD4^+$ subset predominates.

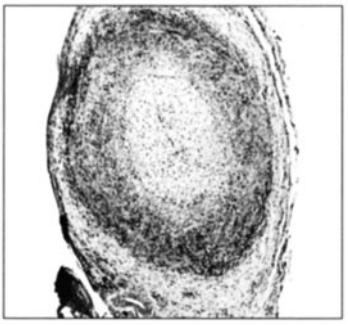
Epidemiology

• The peak age is 60–75 years.

• The female:male ratio is 3:1.

• The annual incidence of biopsy-positive disease is 6.7 in 100 000 people (16.8 in 100 000 >55 years of age).

• The disease occurs predominantly in northern Europe and northern United States.



Occlusion of lumen due to intimal proliferation and inflammation of the media.

Treatment

Diet and lifestyle

• No special precautions are necessary.

Pharmacological treatment

• Patients with giant-cell arteritis should be referred as an emergency to a specialist to arrange a biopsy and to initiate treatment.

• Immediate treatment by a systemic corticosteroid has long been recognized as mandatory in patients with giant-cell arteritis in order to prevent serious vascular complications, particularly blindness.

• Corticosteroids are usually also needed for patients with polymyalgia rheumatica.

• Many patients remain on treatment for years.

• Methotrexate may be helpful in select patients as a steroid-sparing agent.

For polymyalgia rheumatica

Standard dosage Prednisolone, 10–20 mg initially for 1 month, reduced by 2.5 mg every 2 weeks to 10 mg daily, then 1 mg daily every 2–4 weeks; maintenance dose 5–7 mg daily for 6–12 months; final reduction, 1 mg every 4 weeks [6].

Contraindications Systemic infections; caution in pregnancy, hypertension, diabetes mellitus, osteoporosis, glaucoma, epilepsy, peptic ulceration.

Special points In patients whose prednisolone dosage cannot be reduced because of recurring symptoms or who develop serious steroid-related side effects, azathioprine has been shown to have a modest steroid-sparing effect, and methotrexate may be more effective [7].

Main drug interactions Rifampin and phenytoin reduce corticosteroid concentrations; anticoagulant dosage may need adjustment; reduced effect of NSAIDs.

Main side effects Weight gain, edema, increased intraocular pressure, cataracts, glaucoma, gastrointestinal disturbances, peptic ulceration, diabetes, osteoporosis, skin atrophy [8].

For giant-cell arteritis without visual symptoms

Prednisolone, 40–60 mg daily initially for 8 weeks, reduced by 5 mg every 2 weeks to 10 mg daily; then as for polymyalgia rheumatica [9,10].

For giant-cell arteritis with possible or definite ocular involvement

Prednisolone, 60–80 mg daily initially for 8 weeks, reduced to 20 mg daily over next 4 weeks; then as for uncomplicated giant-cell arteritis [9,10].

Treatment aims

To relieve pain and symptoms.
To reduce the incidence of complications.

Prognosis

• Untreated, patients have prolonged ill health, and up to 20% of those with giant-cell arteritis go blind or develop vascular complications.

• Treated, between one-third and one-half of patients can discontinue treatment after 2 years.

Follow-up and management

• Treatment is monitored clinically and by acute-phase response (ESR, CRP).

• Long-term low-dose maintenance prednisolone ≤3 mg, is sometimes needed.

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Postpartum depression

Diagnosis

Definition

• Postpartum depression is defined as a new episode of depression in a woman who has been well for at least the previous 6 months, with onset in the first 90 days postpartum.

• The illness may be manifest later in the puerperium.

Symptoms and signs

Postpartum "blues" [1]

• Develops within first 2 weeks after delivery; peak symptoms occur between 3rd and 7th day after delivery.

Insomnia, anxiety, tearfulness, headaches, irritability, appetite changes, feeling overwhelmed and oversensitive.

• Patients do not meet criteria for major depressive disorder (*see* Depression).

Postpartum depression

• It can occur up to 6 months after delivery; severe cases present early (within the first 6 weeks).

• Patients meet criteria for major depressive disorder (*see* Depression), characterized by depressed mood and/or loss of interest in activities; disrupted sleep and early-morning wakening; psychomotor retardation; or overvalued ideas or delusion of unworthiness, incompetence, and guilt; suicidal thoughts.

• Frequent intrusive, obsessional thoughts of failure as a mother or harm coming to the child are common manifestations.

Postpartum psychosis (bipolar or manic-depressive psychosis)

• Onset is abrupt and occurs between days 3 and 16 in most women. Within a week, a diagnosis of acute severe affective psychosis becomes clear.

Perplexity, agitation, confusion (first few days) followed by hallucinations, delusions, emotional and behavioral disturbances: one-third of patients manifest manic symptoms (overactivity, elation, pressure of speech, flight of ideas), two-thirds manifest depressive symptoms (*see* above).

Investigations

• No special clinical investigation is needed beyond the normal physical postpartum investigations, including history, physical examination, and hemoglobin and thyroid-stimulating hormone levels.

Complications

Delayed detection and treatment of severe depression, physical morbidity.

Suicide and infanticide: rare but tragic and often avoidable.

Failure to establish relationship with child.

Removal of child by family or social services.

Lasting problems in child's social, emotional, and cognitive development and physical health.

Marital difficulties.

Differential diagnosis

Transient hypothyroidism or thyrotoxicosis, profound anemia (fatigue), pituitary or adrenal disorders.

Acute confusional state (delirium, organic brain syndrome): rare, caused by infection, eclampsia, or other neurological disorder.

Distress: caused by social, marital, or relationship problems.

Etiology [2]

• Biological and psychological factors are important.

• No evidence suggests that the hormonal profile of mentally ill mothers differs from that of normal women; the postpartum drop to low progesterone concentrations is probably responsible for the "blues."

• Manic-depressive illness in a first-degree relative indicates a 1 in 3 risk for postpartum psychosis.

• Previous postpartum depression indicates a 1 in 3 risk after subsequent deliveries; previous nonpostpartum depression indicates a 1 in 5 risk or higher.

• Infertility, assisted reproduction, previous obstetric loss, or traumatic delivery may contribute to severe depressive illness.

• Marital conflict, social adversity, lack of confidante, single status, low socio-economic status all increase the risk of a mild depressive episode.

Epidemiology

• 85% of new mothers experience a depressed mood after birth.

• 5%–20% of women who deliver develop postpartum depression.

• Two in 1000 women who deliver are admitted to a psychiatric hospital suffering from a postpartum psychosis.

Treatment [3]

Diet and lifestyle [1]

• Counseling expectant mothers and fathers during the prenatal period about the symptoms and prevalence of postpartum depression will better prepare them for their upcoming roles and occupational changes.

• Expectant mothers should be taught to avoid self-blame if they are unable to meet their expanded responsibilities.

• Stress reduction and family therapy may also help women cope with the emotional and physical demands of their families.

Pharmacological treatment

• Women suffering from severe depression, with active suicidal or infanticidal ideation, and with postpartum psychosis should be treated in an inpatient psychiatric unit.

• Most postpartum depressive illnesses can be managed at home if the patient is not suicidal or infanticidal.

Postpartum "blues"

• Brief in-office counseling and supportive therapy are usually sufficient. Women with complicated social situations (*e.g.*, marital relational problems, threats of domestic violence) will benefit from more intense counseling services from a trained therapist.

Postpartum depression

• Most women (~60%) respond satisfactorily to antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). Both classes of antidepressants are excreted in breast milk, although concentrations are small for SSRIs. Long-term effects on neonates are unknown. Breast-feeding should either be discontinued (especially TCAs) or timed to avoid peak concentrations (SSRIs).

• Excessive sedation should be avoided because of childcare responsibilities.

• Women should always be referred to a psychiatrist if they are severely distressed, in a state of hopeless despair, or suicidal. *See* Depression *for details.*

Postpartum psychosis

• The immediate priority is to sedate the patient with neuroleptics to a level that makes her safe, allows adequate nutrition, and reduces her agitation, confusion, and fear.

• Treatment often requires both antipsychotic and antidepressant medication.

Standard dosage	Haloperidol, 5–20 mg daily orally for acute psychosis; alternatively risperidone, 1–3 mg twice daily.
Contraindications	*Neuroleptics:* hypersensitivity; caution in cardiovascular disease, hepatic impairment, epilepsy.
Special points	If no response occurs within 7 days, electroconvulsive therapy or lithium carbonate can be tried. Postpartum women are very sensitive to the extrapyramidal side effects of neuroleptic agents; close monitoring is needed. SSRIs and TCAs take effect in 10–14 days. No psychotropic drug is of proven safety in breast-feeding.
Main drug interactions	*Neuroleptics:* antagonize anticonvulsants.
Main side effects	*Neuroleptics:* sedation, extrapyramidal effects, acute dystonias, akasthesia, parkinsonism.

Treatment aims

To provide early detection and prompt treatment in the setting most appropriate for safe recovery.

To give priority to the needs of the baby.

To avoid unnecessary separation of mother and baby.

To provide social and psychological support.

Psychosocial treatment

Adjunctive psychotherapy and specific counseling for all patients.

• Nondirective or cognitive therapy (6 sessions at weekly intervals) is effective for mild depressive illness.

• Practical social support and addressing of concurrent problems are essential.

• Psychosocial treatment is as effective as antidepressants for mild depressive illness.

Prognosis

• With early intervention and effective treatment the prognosis is excellent; improvement begins within 2 weeks and recovery within 6–8 weeks.

• Without treatment the illness may be prolonged, although 60% of patients recover spontaneously within 6 months.

Follow-up and management

• Treatment should continue for at least 6 months after the patient has recovered, longer in the case of a relapse.

• Patients with previous manic-depressive episodes should take lithium or valproic acid.

• For serious mental illness, the risk follows every childbirth: 1 in 3–5 risk of recurrent postpartum depression.

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Postpoliomyelitis syndrome

Diagnosis

Symptoms

In patients with known prior poliomyelitis infection:

Neuromuscular symptoms such as pain, cramps, myalgia, arthralgia (post-polio syndrome).

Weakness, slowly progressive (54% to 87% previously affected muscles; 33% to 77% previously unaffected), muscle atrophy, fatigue (PPMA).

Lower extremities affected more frequently than upper.

Dysarthria, dyspnea in 42%.

Symptoms begin 20–40 years after initial polio infection.

Signs

In patients with known prior poliomyelitis infection:

Weakness, atrophy, fasciculations.

Hyperreflexia, extensor plantar responses.

Spasticity (rare).

Sensation should be unaffected.

Investigations

Electromyography: confirm denervation in affected, unaffected muscles, find evidence (giant motor units) of prior polio, and exclude other neuromuscular disorders.

Erythrocyte sedimentation rate, thyroid function tests, creatine kinase.

Radiographs as indicated for arthralgias.

Pulmonary function tests, swallowing studies as indicated by symptoms.

The following do not add to specificity of diagnosis, may be needed to exclude other considered diagnoses:

Muscle biopsy confirms prior denervation; spinal fluid examination reveals normal routine studies.

Viral assays.

Complications

Sleep apnea (central and obstructive), joint derangements (in 60%, due to lack of support by weakened muscles), falls, aspiration, choking.

Differential diagnosis

Confirm history of polio. Diagnosis of exclusion.

Neuromuscular disorders producing similar symptoms: polyneuropathy, myopathy, myasthenia gravis, spinal cord disease, spinal stenosis, polyradiculopathy, nerve entrapments (*e.g.*, carpal tunnel syndrome).

Musculoskeletal disorders producing similar symptoms: arthritis, tendonitis, polymyalgia rheumatica, fibromyalgia.

Central nervous system disorders producing similar symptoms: multiple sclerosis.

Other disorders producing fatigue and weakness: hypothyroidism

Differentiate from ALS by slow rate of progression.

Epidemiology

First recognized in 1875. Estimated > 600,000 in United States with history of paralytic poliomyelitis and thus at risk. Develops in 22% to 68% of exposed patients.

Last US "wild" case was 1979; last case in Americas in Peru, 1991.

Eight vaccine-related cases of polio per year.

Number of potential patients decreasing yearly.

No increased risk of motor neuron disease after polio.

Treatment

Diet and lifestyle

Avoid obesity.
Altered food consistency may be required if progressive dysphagia present.

Pharmacological treatment

Anecdotal and open label reports have suggested amantadine and pyridostmine to treat fatigue and weakness, respectively. No significant improvement in controlled trials. Creatine has been shown effective in slightly improving neuromuscular weakness and fatigue.

High-dose steroids and insulin-like growth factor (IGF-1) are ineffective.

Nonsteroidal antiinflammatory agents for arthralgia.

Nonpharmacological treatment

Nonfatiguing exercise, reconditioning, stretching.

Bracing of weak limbs (*e.g.*, ankle foot orthosis for foot drop), assistive devices as needed.
Percutaneous feeding tubes for severe dysphagia (rarely required).

Treatment aims

Maintain function and fitness; overcome weakness with bracing, assistive devices.
Energy-saving principles to avoid fatigue.

Prognosis

Weakness progresses only slowly if at all; summed MRC decreases 1%/year.

Follow-up and management

Follow-up to exclude more rapid decline or other finding suggesting alternative diagnosis.
Physical therapy to maintain joint range of motion.
Continued evaluation for assistive devices as weakness progresses.
Monitor changes in ventilatory function in those with dyspnea.

General references

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Pressure ulcers

Diagnosis

Symptoms and signs

• Pressure ulcers should be assessed for location; stage (*see* table); size; presence of sinus tracts, undermining, tunneling, exudate, necrotic tissue, and granulation tissue or epithelialization.

• Characteristics should be thoroughly documented.

• Pain associated with pressure ulcers should be assessed and treated with analgesics while the ulcer is healing.

Pressure ulcer staging

Stage I	Nonblanchable erythema of intact skin
Stage II	Partial-thickness skin loss involving epidermis and/or dermis; the ulcer is superficial and appears as an abrasion, blister, or shallow crater
Stage III	Full-thickness skin loss involving damage or necrosis of subcutaneous tissue superficial to fascia; appears as deep crater with or without undermining of adjacent tissue
Stage IV	Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, tendon, or joint capsule; undermining and sinus tracts may be present

Risk factors

Bed- and chair-bound status: especially with impaired ability to reposition.

Incontinence: fecal incontinence presents greater risk than urinary incontinence.

Poor nutritional status: albumin <3.5 mg/dL, total lymphocyte count <1800, patient not eating, weight <80% of ideal body weight. Vitamin deficiencies are common among nursing home residents and may contribute to ulcer formation and persistence.

Chronically moist or dry skin.

Friction and shear forces: pressure lateral to surface of the skin, as when repositioning patients by sliding or when patients sit up in bed without foot support.

• Risk assessment should be carried out periodically among patients with one or more risk factors. Serial use of assessment scales such as the Norton Scale (*see* table) help to measure patients' degree of risk and identify changes in risk status over time.

Norton scale*

Physical condition	Mental condition	Activity	Mobility	Incontinent
Good = 4	Alert = 4	Ambulant = 4	Full = 4	Not = 4
Fair = 3	Apathetic = 3	Walk with help = 3	Slightly limited = 3	Occasional = 3
Poor = 2	Confused = 2	Chair-bound = 2	Very limited = 2	Usually (urine) = 2
Very bad = 1	Stupor = 1	Bed-bound = 1	Immobile = 1	Doubly = 1

*Scores are the total of individual scales (range, 5–20).

Investigations

Swab cultures: reflect surface colonization and have no diagnostic value.

Needle aspiration or tissue biopsy: should be used when necessary to obtain cultures.

Plain radiograph of underlying bone and nuclear medicine bone scan: for nonhealing pressure ulcers under appropriate treatment, may help diagnose underlying osteomyelitis.

Complications

Osteomyelitis, bacteremia, advancing cellulitis: most common.

Endocarditis, heterotopic bone formation, maggot infestation, meningitis, perineal-urethral fistula, squamous cell carcinoma in the ulcer, sinus tract, or abscess formation: less common.

Differential diagnosis

• Commonly overlooked causes of nonhealing ulcers include underestimate of ulcer stage, underlying osteomyelitis, and other complications such as squamous cell carcinoma (see Complications).

• Pyoderma gangrenosum (rapidly expanding ulcer; may be associated with inflammatory bowel disease or other causes, or may be idiopathic).

• Ecthyma gangrenosum (neutropenic patients; usually due to *Pseudomonas* infection).

Etiology

• Pressure ulcers occur as a result of inadequate blood flow to capillaries in soft-tissue beds, in part due to mechanical pressure over the involved area.

• Tissue-threatening compromise of microvessel blood flow is a function of both pressure and time, and can occur as a result of high pressures for brief periods (e.g., sitting on ischial tuberosities), low pressure for prolonged periods (e.g., heel pressure in bedbound patients), or both (e.g., trochanteric pressure in bed-bound patient).

Epidemiology

• Pressure ulcers occur in 10% of hospitalized patients; 20%–25% of nursing home residents; 60% of hospitalized quadreplegic patients; 66% of elderly patients admitted to hospitals for femoral fracture.

• 25% of nonhealing pressure ulcers are associated with underlying osteomyelitis.

• Total annual national cost of pressure ulcer treatment is estimated at $1.3 billion.

Treatment

Diet and lifestyle

Prevention

• Minimize risk factors through skin care, ensuring adequate dietary intake, maximizing mobility.

• Skin massage over bony prominences may lead to deep tissue trauma and thus should not be used.

• Reposition patients at risk at least every 2 hours, using a written schedule. Because of higher pressure loads, seated patients must be repositioned every hour, by returning to bed if necessary. Seated patients who are able should be taught to reposition themselves every 15 minutes.

• Pillows or foam wedges should be used to keep bony prominences (knees, ankles) from direct contact with one another.

• Patients who are completely immobile should have a care plan that includes the use of devices that totally relieve pressure on the heels (*e.g.*, by raising them off the bed).

• Static support surfaces (foam rubber, "egg-crate" cushions) are helpful in patients who can be periodically repositioned (or reposition themselves). Doughnut cushions should be avoided.

Debridement

• Devitalized tissue should be removed. Sharp debridement is necessary with advancing cellulitis or sepsis. Debridement by a surgeon is indicated for large ulcers or if the primary physician is inexperienced. Mechanical (*e.g.*, wet-to-dry dressings, hydrotherapy, wound irrigation, and dextranomers) or enzymatic (*e.g.*, collagenase) debridement is effective for small wounds.

Wound cleansing

• Normal saline should be used to cleanse most wounds, initially at each dressing change. Antiseptic agents and skin cleansers are cytotoxic to normal tissues and should generally be avoided. Wound should be irrigated under mild pressure (*e.g.*, syringe with 19-gauge needle), adequate to remove bacteria and debris. Whirlpool treatment may be necessary for thick exudate, slough, or necrotic tissue.

Wound dressing

• After debridement and wound cleansing, moist dressings (*e.g.*, continuously moist saline gauze, hydrocolloid dressing such as Duoderm) are preferable to dry dressings.

• Dynamic support surfaces (air-fluidized, low-air loss, and alternating air support devices) are expensive but should be considered in patients with stage III or IV pressure ulcers on multiple turning surfaces.

Pharmacological treatment

• Stage II, III, and IV pressure ulcers are uniformly colonized with bacteria. Colonization per se need not (and should not) be treated with antimicrobial agents. Minimizing bacterial colonization enhances healing, however, and is best achieved through wound debridement and cleansing (*see* Wound dressing).

• Wound infection (purulence, foul odor) is initially managed by increasing the frequency of wound cleansing.

• For infected ulcers that produce exudate after 2–4 weeks of aggressive wound cleansing, or appear clean but nonhealing, a 2-week trial of a topical antibiotic is appropriate. The antibiotic should be effective against gram-negative, gram-positive, and anaerobic organisms (*e.g.*, silver sulfadiazine, triple antibiotic). If resistant staphylococcal organisms are prevalent in the nursing home, mupirocin ointment should be used and susceptibility demonstrated.

• Choice of topical antimicrobial agents can be guided by culture of material obtained through needle aspiration or biopsy of ulcer tissue. Swab cultures are not helpful in guiding therapy, because all open pressure ulcers are colonized with bacteria.

• Appropriate systemic antibiotic therapy should be given for patients with bacteremia, sepsis, advancing cellulitis, or osteomyelitis. Systemic antibiotics are not required for pressure ulcers with clinical signs only of local infection.

Treatment aims

To achieve complete healing.

To provide patient comfort (in terminal illness).

Other treatments

• Electrical stimulation therapy, using proper equipment and trained personnel, may be helpful for stage III and IV and recalcitrant stage II ulcers.

• Hyperbaric oxygen, infrared, ultraviolet, and low-energy laser irradiation, and ultrasound therapy have not been demonstrated to be of benefit.

• Various topical treatments (sugar, vitamins, hormones), growth factors, and skin equivalents have not been demonstrated to be of benefit.

• Operative repair (*e.g.*, skin grafts, skin flaps, musculocutaneous flaps) should be considered for clean stage III or stage IV pressure ulcers not responding to optimal care.

• Vitamin C and zinc nutritional supplements may aid healing in the presence of deficiencies.

• Research on exogenous growth factors to accelerate the healing process is being done.

Prognosis

• A clean pressure ulcer should show evidence of some healing within 2–4 weeks. If no progress can be demonstrated, re-evaluate the adequacy of the overall treatment plan as well as adherence to the plan, including risk factor modification.

Follow-up and management

Monitor at least weekly, with documentation of pressure ulcer characteristics and revision of management plan as appropriate.

General references

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Pressure Ulcers in Adults: Treatment. Rockville: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services; 1994. [AHCPR Publication 94-0075.]

Diagnosis

Symptoms

• Many prostate cancers are asymptomatic at the time of diagnosis; initiated by an elevation in a serum prostate-specific antigen (PSA) screening study.

Urinary hesitancy, frequency, urgency, incontinence.

Decreased urinary stream.

Nocturia.

Signs

Presence of induration, enlargement, or a discrete mass within the prostate on digital rectal examination.

Bone pain (metastatic disease).

Investigations

For screening [1,2]

• Serum PSA is frequently used as a screening assay. However, there is no universally acceptable role for screening because of the inability to identify patients who will develop clinically significant disease and to balance these patients with those who will undergo unnecessary therapeutic interventions for clinically insignificant neoplasms.

For diagnosis

• The need to pursue a diagnosis of prostate cancer depends on symptoms, findings on physical examination, and identification of an elevated serum PSA level.

Digital rectal examination: only 25%–50% of men with an abnormal examination will have prostate cancer.

Transrectal ultrasonography.

Transrectal ultrasonography–guided transrectal needle biopsy.

PSA determination.

Prostatic acid phosphatase: less valuable since PSA was discovered.

Bone scanning: when metastatic disease to bone is suggested.

Computed tomography and magnetic resonance imaging: not useful for diagnosis but may be helpful in specific circumstances.

Staging: Tumor staging systems, such as the TNM and American Urologic Association (AUA) staging systems, define the extent of disease within and beyond the prostate gland.

AUA Staging System

Stage A	Tumor found incidentally at transurethral retrograde prostatectomy.
Stage B	Tumor(s) confined to the prostate gland.
Stage C	Tumors that have extended through the glands' capsule.
Stage D	Tumors that have spread to regional lymph nodes or to distant sites.

Complications

Pain, metastases to bone, urinary tract infection, spinal cord compression, benign prostatic hypertrophy.

Differential diagnosis

Benign prostatic hypertrophy.

Transitional cell carcinoma.

Small cell tumors.

Carcinosarcoma.

Lymphoma.

Germ cell tumors.

Mesenchymal neoplasms.

Etiology

Inactivation of several tumor suppressor genes (*e.g., p53, RB*) and overexpression of oncogenes (*e.g., H-ras, bcl-2*) have been implicated in prostate carcinogenesis.

Epidemiology

The incidence of a diagnosis of prostate cancer is increasing.

Median age at diagnosis in the United States is 66 years.

Prostate cancer is responsible for 36% of newly diagnosed cancers and is the second leading cause of cancer deaths in men.

Increasing risk with age: although it is estimated that 70% of men older than 80 years of age have some histologic evidence of prostate cancer, many of these cancers never become clinically evident or significant.

Histologic grading

Determines the biologic potential of the tumor.

Gleason grading system is the one most commonly used. A score of 1–5 is assigned for the primary and secondary growth patterns of a tumor; a score of 1 represents the most differentiated, with discrete gland formation; a score of 5 represents very undifferentiated tumors, with nearly complete loss of glandular structures. The two scores are added together to give a total of 2–10. The higher the score, the more likely the presence of extracapsular spread, lymph node involvement, and eventual metastases.

Treatment [3–5]

Diet and lifestyle

- Patients should be encouraged to live as normal a life as possible.
- Counseling for patients and their sexual partner may be needed for changes in sexual function associated with therapy.

General principles

- Type of treatment depends on disease stage, age of the patient, and biologic behavior of the tumor.
- Treatment should be given under specialist supervision.

Surgical treatment

- Surgery is mainstay of therapy for organ-confined disease and for relieving symptoms related to prostate gland involvement.
- Many surgical approaches are available. The approach chosen depends on the indication for surgery.
- Pelvic lymph node resections are typically performed during open prostatectomies to assess for involvement by tumor.

Radiation therapy

- A viable alternative to surgery for cure of localized prostate cancer.
- Can be delivered via external-beam or brachytherapy approaches.

Hormonal therapy

- Hormonal therapies primarily used for locoregional and metastatic disease.
- Estrogen (*e.g.*, diethylstilbestrol, fosfestrol), progestational agents (*e.g.*, medroxyprogesterone, megestrol, cyproterone acetate), gonadotropin-releasing hormone analogues (*e.g.*, leuprolide, goserelin), adrenal enzyme synthesis inhibitors (*e.g.*, ketoconazole, aminoglutethimide), and antiandrogens (*e.g.*, cyproterone acetate, megestrol, medroxyprogesterone, flutamide) are used in specific clinical settings.
- Orchiectomy can be considered an alternative form of hormonal therapy.

Chemotherapy

- Primarily reserved for palliation of symptoms in patients with advanced disease.
- Clinical trials are in progress to evaluate and compare old and new agents for effectiveness.

Complications of therapy

Surgery: urinary incontinence, impaired sexual potency.

Radiation therapy: diarrhea, rectal discomfort, rectal bleeding, rectal fistula, rectal perforation, frequency of urination, hematuria, dysuria.

Hormonal therapy: cardiovascular disease, transient exacerbation of prostate cancer symptoms ("flare") with gonadotropin-releasing hormone analogues, somnolence, fatigue, rashes, hypothyroidism, hepatotoxicity, gynecomastia, hot flashes, diarrhea.

Chemotherapy: depends on drug(s) used.

Treatment aims

To provide a cure, when possible.

To alleviate symptoms.

To provide effective palliation when cure is impossible.

Prognosis

Prognosis depends on age at diagnosis, state of disease, and biologic behavior of cancer.

If prostate cancer is organ-confined at the time of diagnosis, it may not have a significant impact on the survival until 10–15 years later.

Follow-up and management

Routine monitoring of PSA level and patient's symptoms is necessary.

Additional interventions with medications or mechanical devices to enhance sexual potency that has been lost because of therapy should be made available when possible.

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Diagnosis

Symptoms

Symptoms of venous or arterial thrombosis.

Signs

• Patients to investigate include those with the following:

Venous thromboembolism before the age of 40–45 years.

Recurrent venous thrombosis or thrombophlebitis.

Thrombosis in an unusual site: *e.g.*, mesenteric vein, cerebral vein.

Unexplained neonatal thrombosis.

Skin necrosis.

Arterial thrombosis before the age of 30 years.

Relatives with a specific defect.

Unexplained prolonged coagulation screening tests.

Recurrent fetal loss, idiopathic thrombocytopenic purpura, SLE.

Investigations

• Functional and immunological assays are needed for a precise diagnosis.

• Screening tests and functional assays should be performed on fresh citrated blood samples collected with minimal venous stasis on all patients being investigated for a prothrombotic state.

Complete blood count and film.

Measurement of prothrombin, activated partial thromboplastin, and thrombin time; fibrinogen.

Assays for antithrombin III, protein C, protein S, activated protein C resistance (factor V Leiden), plasminogen, heparin cofactor II, anticardiolipin antibodies, lupus anticoagulant, factor XII, dysfibrinogenemia, homocystinuria, and prothrombin 20210.

Fibrinolytic tests: before and after stimulation (*i.e.*, venous occlusion or DDAVP).

Fibrin plate, tissue-type plasminogen activator, and PA1-1 assays.

Platelet activation markers analysis: *i.e.*, GMP-140 expression, plasma β-thromboglobulin.

Complications

Arterial and venous thrombosis and embolism.

Differential diagnosis

Hyperviscosity.

Etiology

Common acquired causes of thrombosis

Diabetes mellitus, hyperlipidemia, malignancy, myeloproliferative disorders, chronic liver disease, SLE, paraproteinemias, nephrotic syndrome, antiphospholipid syndrome.

• These disorders cause predisposition to thrombosis in a multifactorial way; specific homeostatic assays are generally unhelpful in the investigation and management of individual patients.

Inherited defects with increased tendency to thrombosis

Antithrombin III, protein C, protein S, factor V Leiden, plasminogen, heparin cofactor II, factor XII, dysfibrinogenemia, homocystinuria, prothrombin 20210.

• Most of these disorders represent autosomal-dominant traits with variable penetrance.

• Deficiency in the heterozygous state predisposes to thrombosis either spontaneously or in association with other high-risk factors.

Pathophysiology

• The balance of the hemostatic mechanism can be shifted in favor of thrombosis in the following circumstances:

Increased coagulation system activity.
Increased platelet activity.
Decreased fibrinolytic activity.
Damaged vascular endothelial activity.

Epidemiology

• Epidemiological studies have shown an increased incidence of thrombotic events associated with raised concentrations, particularly of fibrinogen, factor VII, and factor VIII:C, with a frequency of 1 in 2000–5000.

High-risk factors for thrombosis

Surgical and nonsurgical trauma.
Age.
Immobilization.
Heart failure.
Prior venous thrombosis and varicose veins.
Paralysis of lower limbs.
Obesity.
Estrogen treatment.
Pregnancy and puerperium.
Smoking.
Raised blood viscosity.

Treatment

Diet and lifestyle

• No special precautions are necessary.

Pharmacological treatment [2]

Prophylaxis for venous thromboembolism [3]

• The degree of risk must be assessed depending on the predisposing factors.

Low risk: early ambulation, graduated compression stocking.
Moderate risk: standard unfractionated heparin, 5000 U s.c. every 8–12 hours.
High risk: low molecular weight heparin, s.c. every 12–24 hours, dose depending on type of heparin.

• The degree of risk for surgical prophylaxis may be defined as follows:

Low risk: <40 years, minor surgery lasting <1 hour.
Moderate risk: >40 years, abdominal or thoracic surgery lasting >1 hour.
High risk: >40 years, knee and hip orthopedic surgery, obesity, and malignancy.

Heparin

Standard dosage [4] Unfractionated heparin, 5000 U i.v. bolus, followed by 1000–2000 U/h i.v.; or 80 U/kg i.v. bolus, followed by 18 U/kg/h i.v., for 5–7 days.
Low molecular weight heparin s.c. once to twice daily [5].

Contraindications Rare hypersensitivity, risk of bleeding complications.

Special points Activated partial thromboplastin time must be monitored 6 hours after start of treatment for unfractionated heparin, then at least every 24 hours, with dose adjustment to maintain ratio at 1.5–2.5 times control.

Main drug interactions Drugs that interfere with platelet aggregation or coagulation.

Main side effects Bleeding, thrombocytopenia, rebound thrombosis, osteoporosis (if treatment lasts >3 months), rare alopecia, skin rash.

• Heparinization can be reversed by administering protamine sulfate, 1 mg, which neutralizes ~100 U heparin; maximum dose, 40 mg i.v. in 10 minutes.

Warfarin [6]

Standard dosage Warfarin, 5 mg orally on days 1, 2, and 3; then adjusted daily according to prothrombin time.

Contraindications Pregnancy.

Special points Prothrombin time must be monitored, with results expressed as INR with therapeutic range of 2.0–4.5.

Main drug interactions Many medications potentiate or antagonize effect; for any new medication, prothrombin time should be checked.

Main side effects Bleeding, skin necrosis after first few days of treatment in the case of protein C or S deficiency.

• Anticoagulant effects can be reversed by an infusion of fresh frozen plasma or factor II, IX, and X concentrate if bleed is life-threatening; vitamin K_1, 1–2 mg i.v., takes 6–24 hours to reverse warfarin effect.

Antiplatelet agents

• These are indicated for prophylaxis and prevention of further arterial thrombotic events when platelet activation has been shown to be a primary pathological factor, particularly myocardial ischemia and cerebrovascular thrombotic strokes, including transient ischemic attack, for secondary thrombocytosis (>800 × 10^9/L), and for essential thrombocythemia.

Aspirin, 75 mg orally daily or 300 mg twice weekly, or dipyridamole, up to 100 mg orally 3 times daily (dipyridamole may cause severe headaches).

Treatment aims

To prevent thrombosis.

Prognosis

• Prognosis depends on the underlying cause and the degree of risk of arterial or venous thrombosis or embolism.

Follow-up and management

• Lifelong expert management is needed.

Therapeutic ranges for oral anticoagulation

INR 2.0–2.5: prophylaxis of deep-vein thrombosis.

INR 2.0–3.0: treatment of deep-vein thrombosis, pulmonary embolism, systemic embolism, prevention of venous thromboembolism in myocardial infarction, mitral stenosis with embolism, transient ischemic attacks, atrial fibrillation.

INR 3.0–4.5: recurrent deep-vein thrombosis and pulmonary embolism, arterial disease including myocardial infarction, mechanical prosthetic heart valves (tissue prosthetic values can be controlled at 2.0–3.0).

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Pruritus

Diagnosis

Symptoms

Uncomfortable sensation provoking the desire to scratch.

Signs

Erythema.
Excoriations.
Lichenification.

Cutaneous disorders associated with pruritus

Inflammatory: atopic dermatitis, lichen simplex chronicus, urticaria, contact dermatitis, lichen planus, drug reaction, seborrheic dermatitis, pityriasis rosea.

Infectious: scabies, pediculosis (lice), pinworms, insect bites/stings, candidiasis, superficial fungal infection, cutaneous bacterial infection, folliculitis, condyloma acuminata.

Immune-mediated: bullous pemphigoid, pemphigus, dermatitis herpetiformis.

Environmental: xerosis, polymorphous light eruption.

Miscellaneous: essential pruritus.

Internal disorders associated with pruritus

Uremia: chronic renal failure (more commonly associated with hemodialysis than peritoneal dialysis).

Liver disease: obstructive biliary disease (primary sclerosing cholangitis, primary biliary cirrhosis, choledocholithiasis, carcinoma, hepatitis C, or drug-induced cholestasis).

Malignancy: Hodgkin's lymphoma (pruritus may precede diagnosis by as much as 5 years); non-Hodgkin's lymphoma; leukemia; mycosis fungoides; multiple myeloma; breast, lung, pancreatic, or gastric carcinoma.

Hematologic: polycythemia rubra vera (pruritus triggered by a sudden drop in temperature), paraproteinemia, rarely in iron deficiency anemia.

Endocrine: hypothyroidism or hyperthyroidism, diabetes mellitus, mastocytosis, carcinoid syndrome.

Neurologic: multiple sclerosis, notalgia paresthetica, cerebral lesions.

Infectious: HIV, viral exanthems (*e.g.*, herpes, varicella), parasitosis.

Psychiatric: depression, neurotic excoriations, severe stress.

Drug-induced: aspirin, morphine, codeine, scopolamine, phenothiazines, anabolic steroids, oral contraceptives, erythromycin estolate, quinidine.

Investigations

- The patient should be questioned and examined for skin lesions to determine the direction of investigation (*i.e.*, cutaneous vs systemic). A careful history regarding the nature of the itch, any new medications, exposures (fiberglass, mites), foreign travel, and the relationship of the pruritus to activities such as bathing should be elicited.
- For suspected systemic sources: complete blood count and differential, liver function tests (including alkaline phosphatase for obstructive disease), renal function testing, thyroid function tests, glucose, and chest radiography.
- Skin scraping: may see mites, ova, or fecal pellets in scabies; hyphae in fungal infection.
- Skin biopsy: useful for some inflammatory cutaneous conditions.
- Patch testing: may be helpful in pruritus caused by contact dermatitis.
- Pediculosis pubis: more than one third of patients have a concurrent sexually transmitted disease and should be tested for such disease.

Complications

Lichenification: from chronic scratching or rubbing.
Secondary infection: of excoriated areas.
Psychological distress: in recalcitrant cases.

Differential diagnosis

Not applicable.

Etiology

- The sensation of pruritus originates from stimulation of nerve endings in the dermoepidermal junction. Free nerve endings connect to unmyelinated C-fibers that carry the impulse to the central nervous systems. Pain and itch share the same neural pathway (spinothalamic tract) but are thought to be distinct sensations.
- An opiate-sensitive scratch center appears to exist at the floor of the fourth ventricle.
- Histamine is the primary chemical mediator, and its release from mast cells can stimulate C-fibers. Other factors (substance P, interleukin-2) may be involved.
- Prostaglandins affect the perception of itch by lowering the threshold of C-fiber response. Serotonin acts on peripheral serotoninergic receptors and opioids can act centrally to induce itch.
- Systemic causes of pruritus are poorly understood. The pruritus of liver disease may relate to the build-up of bile salts in the serum and tissues. Opiate and serotonergic mediators probably play a role. The pruritus of chronic renal failure may involve metabolic derangements due to dialysis or the natural history of renal failure itself. Neurologic disorders can interfere with pathways that modulate pruritus.

Epidemiology

Dry skin is the most common cause of pruritus without primary cutaneous disease.

Systemic disease may be detected in 10%–50% of patients with generalized pruritus; uremia is the most prevalent culprit, with 60%–80% of dialysis recipients experiencing itch.

Treatment

Diet and lifestyle

- Encourage brief lukewarm baths or showers with limited use of mild soaps, followed by liberal use of emollient creams or ointments (more moisturizing than lotions).
- Avoid irritants, *e.g.*, dry ambient environment; contact with wool, fiberglass, fragrances (in detergents and fabric softener); scratching.
- Trimming the fingernails may be of some help.

Pharmacological treatment

- Treatment should be aimed at treating the underlying disease and relieving the itching.

Topical symptomatic relief

Camphor or menthol: 0.25% lotion as needed.

Doxepin: 5% cream up to four times daily; can cause sedation.

Pramoxine hydrochloride: 1% cream up to four times daily; prescription form formulated with 1%–2% hydrocortisone cream.

Low- to mid-potency topical steroids: may be helpful for controlling dermatitis; can cause skin atrophy, hypothalamic pituitary axis suppression, and other sequelae of oral steroid use because of systemic absorption when used for prolonged duration and/or on extensive areas of skin.

Systemic symptomatic relief

Antihistamines (diphenhydramine, hydroxyzine, doxepin): can cause drowsiness, anticholinergic effects.

Nonsedating antihistamines (cetirizine, loratadine, fexofenadine): sometimes helpful.

Corticosteroids (prednisone, dexamethasone): temporary control of an acute flare or recalcitrant disease.

Treatment aims

Treating the underlying disease.

Relieving symptoms.

Other treatments

Uremia: phototherapy, oral activated charcoal, renal transplantation.

Liver disease: cholestyramine, phototherapy, naloxone (parenteral opioid antagonist), ondansetron (5-HT3 antagonist).

Scabies: 5% permethrin cream in infants or adults; 1% lindane cream or lotion in adults; ivermectin, 200 µg/kg single oral dose for resistant cases.

Idiopathic pruritus: capsaicin (substance P antagonist) may be of some help in chronic pruritus; cold stimuli; vibration and transcutaneous electrical nerve stimulation (TENS) are effective short-term therapy; parenteral propofol (subhypnotic doses) inhibits spinal afferents; acupuncture; psychotherapy.

Prognosis

Generally good with treatment of underlying cause.

Follow-up and management

Follow-up should be geared toward treatment of underlying disease states.

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Psoriasis

Diagnosis

Symptoms

Pruritus: in 20% of patients.

Unpleasant odor: in severe extensive cases.

Joint pain, tenderness, and morning stiffness: in cases with psoriatic arthritis.

Chills: secondary to loss of body heat in patients with generalized psoriasis.

Signs

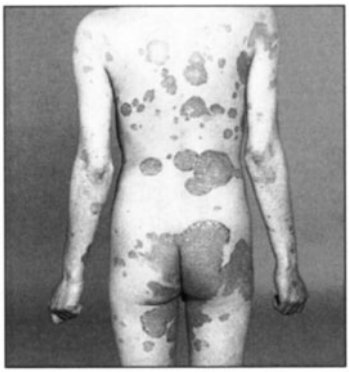
Scalp

Scaling.

Skin

Psoriatic plaques: classic lesion is a red plaque with sharply demarcated borders and a thick, silver scale; most common on elbows, knees, extensor surfaces, and areas of trauma; some patients have pustules (pustular psoriasis); the face is usually spared.

Auspitz sign: removal of scale causes pinpoint bleeding.



Chronic plaque psoriasis. (*See* Color Plate.)

Oral mucosa

Glossitis or geographic tongue: in 10% of patients.

Nails

• 50% of patients have nail involvement.

Pitting.

Subungual keratotic debris.

Onycholysis.

Discoloration: yellow-brown ("oil spots").

Musculoskeletal system

Asymmetrical oligoarticular arthritis: most common. (*See* psoriatic arthritis for more details.)

Investigations

HIV test: if there is a history of sudden onset of severe psoriasis with no family history and no previous personal history.

Antistreptolysin O (ASO) titer: if guttate flare from recent streptococcal infection is suspected.

Complications

Exfoliative erythroderma.

Generalized pustular psoriasis: sheets of sterile pustules and erythema; with associated fever, leukocytosis, arthralgias, skin tenderness, and malaise.

Psoriatic arthropathy.

Ankylosing spondylitis.

Differential diagnosis

Lichen planus.
Tinea corporis.
Seborrheic dermatitis.
Reiter's disease.
Pityriasis rosea.
Secondary syphilis.
Subacute cutaneous lupus erythematosus.
Premycosis fungoides (parapsoriasis).
Drug reaction.
Atopic eczema: especially patients with advanced lichenification.

Etiology

• Psoriasis is a multifactorial disease with a definite genetic predisposition.
Positive family history in 30% of cases.
• Histocompatibility antigen HLA-Cw6 is strongly associated (relative risk of 24).
• The presence of HLA-B17 or B27 is associated with more severe disease or associated arthritis.
• Although immunological abnormalities of humoral and cell-mediated immunity have been described, no specific circulatory immune abnormalities have been identified.
• Epidermal transit time is rapidly increased (6–9-fold).
• Studies have suggested that altered cellular metabolism of vitamin A may play a role.

Precipitating factors

Streptococcal infections.
Trauma: Koebner's phenomenon.
Drugs: beta-blockers, antimalarials, lithium, NSAIDs, oral corticosteroid withdrawal.
Stress.
Sunlight: a small subset of patients actually worsen with sun exposure (especially sunburn).
Alcoholism: may be related to decreased compliance in alcoholic patients.

Epidemiology

• Incidence is 1%–3% of world population [3].
• It affects 2–8 million people in the United States.
• Peak onset is in the second decade of life, but it may appear at any age.

Treatment

Diet and lifestyle

• Avoid physical trauma to the skin.

Pharmacological treatment

• Generalized pustular psoriasis or exfoliative erythroderma should be referred to a specialist immediately.

Topical treatment

Coal tar: safe and effective in plaque psoriasis; messy to apply (limiting compliance).
Steroids: effective and cosmetically acceptable; long-term use needs close supervision.
Vitamin D_3 analogues: calcipotriene appears safe and effective in limited areas of mild to moderate psoriasis; may be irritating on the face.
Phototherapy: ultraviolet B useful for chronic plaque and guttate psoriasis, alone or with other treatments such as topical applications.
Tazarotene (a recently developed receptor-selective retinoid): efficacious in mild to moderate plaque psoriasis. Once-daily application of a 0.1% or 0.05% gel.
Tazarotene: applied once daily in conjunction with a potent topical steroid; often leads to local irritation; contraindicated during pregnancy.
Anthralin: 0.1% to 1% cream, applied once daily; not recommended for use on face or acutely inflamed lesions; may be irritating and can cause skin and hair discoloration.

Systemic therapy

• Treatment should be given under supervision of a specialist.
• Long-term photochemotherapy is complicated by increased risk of cutaneous squamous cell carcinoma.

Standard dosage	Determined by specialist with systemic therapy experience.
Contraindications	*Acitretin:* childbearing potential, pre-existing hepatic disease, hypertriglyceridemia. *Methotrexate:* history of hypersensitivity to drug, hepatic disease, alcohol abuse, pregnancy. *Cyclosporine:* hypertension, renal insufficiency, underlying systemic infection.
Special points	*Acitretin:* effective in acral or generalized pustular psoriasis; teratogenic potential is present for up to 3 years after drug cessation. *Methotrexate:* oral or i.m.; used in widespread plaques, acute generalized pustular psoriasis, erythrodermic psoriatic arthropathy; should first be given with test dose; monitor CBC, liver function tests, periodic liver biopsy, depending on total dosage ingested. *Cyclosporine:* best for short-term treatment of erythrodermic or pustular psoriasis; side effects limit long-term use; may be used for severe refractory psoriasis, psoriatic arthropathy; monitor blood pressure, serum creatinine levels, creatinine clearance.
Main drug interactions	*Methotrexate:* trimethoprim–sulfamethoxazole, alcohol, NSAIDs, probenecid, retinoids. *Cyclosporine:* use caution with medications that affect renal function and drugs that inhibit the cytochrome P-450 system.
Main side effects	*Acitretin:* drying of skin and mucosa, elevated liver enzyme and triglyceride levels, myalgias, teratogenicity. *Methotrexate:* gastrointestinal, bone marrow suppression, immunosuppression, dose-dependent risk for hepatic fibrosis/cirrhosis, teratogenic effects, abortifacient. *Cyclosporine:* dose-dependent hypertension and nephrotoxicity, electrolyte imbalances, immunosuppression.

Alternative medicine

Recommended: none.
Common use: angelica (*Angelica archangelica*); cleavers (*Gallium aparine*); Yellow dock (*Rumex crispus*); figwort (*Scrophularia nodosa*); gotu kola (*Centella asiatica* or Hydrocotyle).
Caution: none.

Treatment aims

To control and prevent severe disease.

Prognosis

• Psoriasis is usually a chronic disease characterized by flares and remissions.

Follow-up and management

Individualized for each patient.

General references

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Pubertal abnormalities

Diagnosis

Symptoms

Precocious puberty

Pubertal development <8 years in girls, <9 years in boys.

Rapid growth.

Menstruation in girls.

Advanced skeletal maturation.

Behavioral disturbance.

Delayed puberty

Lack of pubertal development >14 years in girls, >15 years in boys.

Lack of pubertal growth spurt.

Small external genitalia in boys.

Possible anosmia.

Social difficulties.

Signs

Precocious puberty

Secondary isosexual sexual development.

Tall stature.

Short stature.

Cutaneous pigmentation: McCune–Albright syndrome.

Acne, clitoromegaly: indicating virilization in girls.

Delayed puberty

Lack of secondary sexual development.

Gynecomastia in boys.

Family history of delayed puberty.

Signs of Turner's syndrome in girls.

Chronic pediatric illness: *e.g.*, Crohn's disease, thalassemia.

Investigations [1,2]

Precocious puberty

Usually divided into gonadotropin-dependent (hypothalamic or pituitary) or gonadotropin-independent (*see* Etiology).

Hormone measurement: for gonadotropin and sex steroid concentrations.

MRI or CT of hypothalamic–pituitary region: to exclude structural lesion.

Ovarian ultrasonography: to assess ovarian development.

Adrenal CT: for precocious puberty secondary to adrenal tumors.

Delayed puberty

Hormone measurement: for gonadotropin and sex steroid concentrations.

Complete blood count, electrolytes analysis, liver function tests: to exclude chronic disease.

Karyotyping: in girls.

MRI or CT of hypothalamic–pituitary region: to exclude structural lesion.

Ovarian ultrasonography: to assess ovarian development.

Test of smell: to exclude Kallmann's syndrome.

Clomiphene test: in older patients, to exclude gonadotropin-releasing hormone deficiency.

Complications

Precocious puberty

Progression of pubertal development.

Early menstruation.

Premature completion of skeletal maturation.

Adult short stature.

Delayed puberty

No secondary sexual development.

Absence of pubertal growth spurt.

Emotional, physical immaturity.

Infertility.

Differential diagnosis

Not applicable.

Etiology [1,2]

True precocious puberty (gonadotropin-dependent)

Idiopathic (principally girls).
Structural lesions of hypothalamic region (tumors).
Postcranial irradiation.
Hydrocephalus.
Hypothyroidism.

Pseudoprecocious puberty (gonadotropin-independent)

McCune–Albright syndrome.
Familial male precocious puberty.
Adrenal tumors.
Congenital adrenal hyperplasia.
Gonadal tumors.
Human chorionic gonadotropin–secreting tumors.
Exogenous sex steroids.

Delayed puberty

Constitutional.
Chronic pediatric illness.
Malnutrition.
Hypopituitarism (idiopathic, tumors).
Isolated gonadotropin-releasing hormone deficiency and anosmia (Kallmann's syndrome).
Hyperprolactinemia.
Intensive exercise.
Turner's or Klinefelter's syndromes.
Radiotherapy, surgery, chemotherapy, autoimmunity.

Epidemiology

- No reliable estimates are available.

Treatment

Diet and lifestyle

• No special precautions are necessary.

Pharmacological treatment [1,2]

Should be carried out in conjunction with an appropriate specialist.

For central precocious puberty

• Primary CNS lesions, *e.g.*, tumors, must be treated.

Gonadotropin-releasing hormone analogue fixed dose s.c. injection monthly or cyproterone acetate, 50–100 mg daily; treatment continued until appropriate age for puberty to progress.

• Long-term cyproterone treatment may induce adrenal insufficiency.

For gonadotropin-independent precocious puberty

Treatment of underlying disease (*e.g.*, congenital adrenal hyperplasia).

Androgen antagonists (spironolactone).

Inhibitors of steroid synthesis (ketoconazole).

For delayed puberty

• The primary cause must be treated, *e.g.*, chronic illness, pituitary tumor, hyperprolactinemia.

For boys: testosterone, from 50 mg every 2 weeks to 300 mg every 3 weeks i.m. depending on age.

For girls: ethinyl estradiol, 2–10 μg daily, increasing to 30 μg daily with norethindrone or medroxyprogesterone acetate, 5 mg daily on days 1–14 of each calendar month.

Treatment aims

To replace hormones.

Prognosis

• Prognosis is good unless the disorder is caused by a tumor.

Follow-up and management

• Patients should be checked every 3–6 months to ensure that treatment is effective.

Key references

1. Bridges NA, Brook CDG: Premature sexual development. In *Clinical Endocrinology.* Edited by Grossman A. Oxford: Blackwell Scientific Publications; 1992:837–846.
2. Stanhope R, Albanese A, Shalet S: Delayed puberty. *BMJ* 1992, **305**:790.

Pulmonary complications of immunosuppression

Diagnosis

Symptoms

• Symptoms may be minimal.

Dyspnea, cough, sputum production, hemoptysis, chest pain, weight loss, fever.

• Hemoptysis with chest pain suggests Kaposi's sarcoma in those with AIDS but pneumonia in those with other forms of immunosuppression.

Signs

Tachypnea.

Cyanosis: indicating respiratory failure.

Consolidation: suggesting bacterial infection.

Collapse: suggesting infection or neoplasia.

Pleural effusion: suggesting mycobacterial infection or neoplasia.

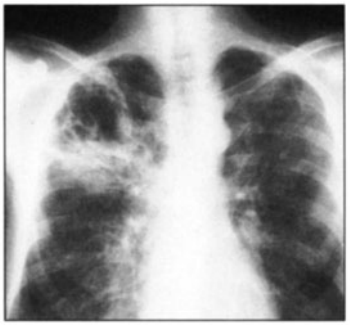
Investigations

• The choice of investigation depends on the physical signs and symptoms and the degree of immunosuppression.

To assess degree of immunosuppression

Complete blood count, differential leukocyte count: in patients with acquired immunosuppression, *e.g.*, to assess neutropenia, after organ transplantation.

Immunoglobulin measurement, CD4 count: in patients with acquired immunosuppression; normal CD4 count in early stages of HIV infection, bacterial infection common; low CD4 count in late stages of HIV infection, opportunistic infection or neoplasia more likely.



Chest radiograph showing cavitating aspergilloma.

To assess pulmonary complications of immunosuppression

Chest radiography: to identify focal or generalized abnormality.

CT: to assess pulmonary abnormalities in more detail (*e.g.*, intrathoracic lymph nodes).

Oximetry or arterial blood gas measurement: at rest or exercise, essential for early detection of respiratory failure.

Sputum for special stains and cytology: in patients with nonproductive coughs, sputum may be induced by inhalation of 3% nebulized saline solution.

Bronchoscopy, bronchoalveolar lavage, transbronchial biopsy, open lung biopsy: for tissue diagnosis.

Mediastinoscopy: if mediastinal lymph-node disease has been identified.

Complications

Respiratory failure.

Disseminated infection.

Disseminated secondary malignancy.

Differential diagnosis

• The diagnosis depends on the course, stage, and degree of immunosuppression, in addition to local pathogenic load, which may differ in community, hospital, or geographical location.

P. carinii pneumonia (*see Pneumocystis carinii pneumonia in AIDS for details*).

Bacterial infection (including mycobacteria).

Viral infection (*e.g.*, cytomegalovirus).

Fungal infection (*e.g.*, aspergillus, candida).

Parasitic infection (*e.g.*, *Strongyloides*).

Kaposi's sarcoma.

Secondary B cell lymphoma.

Secondary carcinoma.

Lymphocytic interstitial pneumonitis.

Graft-versus-host disease or rejection episodes in transplant recipients.

Etiology

Congenital causes

Genetically determined absence or reduction in immune response, *e.g.*, X-linked infantile hypogammaglobulinemia (Bruton type).

Acquired causes

HIV infection.

Organ transplantation.

Drug treatment, *e.g.*, steroids, azathioprine, cyclosporine (used in rheumatoid arthritis, asthma, ulcerative colitis).

Causes of relative immunosuppression

Diabetes.

Old age.

Epidemiology

• 1 in 100 000 people suffers from congenital immunosuppression.

• The incidence of acquired immunosuppression is increasing with the use of immunosuppressive drugs, organ transplantation, and HIV infection.

Treatment

Diet and lifestyle

• Excessive alcohol consumption should be avoided.

• Cigarette smoking should be stopped because of the increased incidence of pulmonary complications in immunosuppressed patients who smoke.

Pharmacological treatment

• Treatment depends on diagnosis, which should be as accurate as possible.

• In deteriorating patients, treatment must be started empirically, depending on the most probable cause or agent; this is determined by the combination of symptoms, signs, degree of immunocompromise, stage of immunocompromise, and local pathogenic load.

Antibiotics

• If a specific organism is not detected and the patient is deteriorating, antibiotics may be used when there is purulence on the Gram stain.

Antituberculous drugs

• Four-drug treatment (ethambutol, rifampin, pyrazinamide, isoniazid) is recommended until sensitivity is available.

Antiviral agents

• Treatment should be initiated only if diagnosis is established.

For cytomegalovirus disease: Ganciclovir, 6 mg/kg twice daily initially, then maintenance dose depending on response.

Foscarnet, 90 mg/kg continuous infusion over 90 minutes twice daily depending on renal function.

• Renal function and leukocyte count must be monitored.

Antifungal agents

• Treatment should be initiated only if diagnosis is established.

Amphotericin B, 0.5 mg/kg daily i.v., increasing to 1 mg/kg daily, depending on renal function.

Itraconazole, 200 mg daily.

Antiparasitic agents

Trimethoprim, 15 mg/kg, may be used for *Pneumocystis* spp. infection.

Chemotherapy

• Chemotherapy may be used in certain patients with Kaposi's sarcoma or secondary B cell lymphoma or carcinoma.

• The choice of treatment is determined locally, and the use of chemotherapy combined with radiation therapy for symptomatic treatment must be considered.

Treatment aims

To eradicate infection and to prevent recurrence.

To relieve symptoms of secondary neoplasia or Kaposi's sarcoma.

Other treatments

Controlled oxygen therapy.

Continuous positive airways pressure.

Mechanical ventilation: needs careful consideration, ideally with the patient or a relative, before initiation.

Prognosis

• Prognosis depends on the cause of immunosuppression and the form of pulmonary complication.

• Mortality is 10%–20% in transiently neutropenic patients with bacterial infection.

• If the immunosuppression is reversible, recurrence is unlikely after the patient has recovered from an acute event.

Follow-up and management

• In continuing immunosuppression, follow-up and management depend on the specific diagnosis: for example, HIV-infected patients may need prolonged prophylactic treatment against recurrence of *P. carinii* infection.

General references

Dichter JR, Levine SJ, Shelhamer JH: Approach to the immunocompromised host with pulmonary symptoms. *Hematol Oncol Clin North Am* 1993, **7**:887–912.

Lartholory O, Dupont B: Antifungal prophylaxis during neutropenia and immunodeficiency. *Clin Microbiol Rev* 1997, **10**:477–504.

Verra F, *et al.*: Bronchoalveolar lavage in immunocompromised patients: clinical and functional consequences. *Chest* 1992, **101**:1215–1220.

Wade JC: Treatment of fungal and other opportunistic infections in immuno-compromised patients. *Leukemia* 1997, **11(suppl 4)**:S538–S539.

Pulmonary embolism

Diagnosis

Symptoms

Pleuritic chest pain, dyspnea, hemoptysis: indicate acute minor pulmonary embolism.

Acute-onset dyspnea, syncope, central chest pain: indicate acute massive pulmonary embolism.

Gradual-onset dyspnea, pleuritic chest pain, decreasing exercise tolerance: indicate subacute massive pulmonary embolism.

Increasing dyspnea, effort syncope: indicate chronic pulmonary embolism.

Signs

• Pulmonary embolism manifests in several ways, depending on extent of pulmonary vascular obstruction, time during which obstruction accumulates, presence/absence of preexisting heart or lung disease.

Shortness of breath, pleural rub, signs of pleural effusion: indicate pulmonary infarction.

Tachypnea or hyperventilation, reduced cardiac output, right heart failure: indicating massive pulmonary embolism.

Evidence of right ventricular dysfunction: bulging neck veins with V waves, left parasternal lift, accentuated pulmonic component of S2, systolic murmur at the left lower sternal border that increases in intensity during inspiration; may be obscured by obesity or barrel-shaped chest. Bulging neck veins may be replaced by profound hypoxemia when right-to-left shunting occurs through a patent foramen ovale.

Pulmonary hypertension: indicating chronic pulmonary embolism.

Investigations

• The diagnosis of pulmonary embolism needs a high index of clinical suspicion, combined with the results of investigations that may confirm or refute these suspicions.

• Combining noninvasive diagnostic tests may be useful. A normal D-dimer ELISA and venous ultrasonography can help rule out pulmonary embolism; echocardiography showing right ventricular hypokinesis combined with positive findings on ultrasonography of legs is virtually pathognomonic of pulmonary embolism.

D-dimer ELISA and venous Doppler ultrasonography: useful when clinical likelihood is low. D-dimer ELISA lacks specificity but is best suited for the emergency department or physician's office when the patient does not have associated systemic illnesses. The assay usually requires 3–4 hours to perform.

Pulmonary angiography: allows definitive diagnosis; invasive; needs specialized facilities.

Chest radiography: focal oligemia (Westermark's sign), a peripheral wedge-shaped density over diaphragm (Hampton's hump), enlarged right descending pulmonary artery (Palla's sign).

ECG: T-wave inversion in anterior leads, especially V1–V4. Probably reciprocal changes reflecting inferoposterior ischemia due to compression of the right coronary artery by the right ventricle as a result of pressure overload. Sinus tachycardia usual. New-onset right bundle-branch block or atrial fibrillation uncommon. The classic S1, Q3, T3 pattern nonspecific and unusual.

Perfusion scanning: Normal results are associated with recurrent pulmonary embolism, even if anticoagulants are withheld. Whereas normal results or results indicating a high probability of disease are extremely helpful, nondiagnostic results are difficult to interpret. Only rarely does ventilation scanning clarify the interpretation of perfusion lung scans.

Spiral CT of chest with contrast: best suited for pulmonary embolism in the proximal pulmonary vascular tree. However, if there is strong suspicion, contrast pulmonary angiography that focuses on distal pulmonary vasculature should be performed.

Gadolinium-enhanced magnetic resonance pulmonary angiography: reveals anatomical features and assesses right ventricular function.

Echocardiography: About 40% of patients with pulmonary embolism have right ventricular abnormalities. Useful to identify aortic dissection or pericardial tamponade, which may mimic pulmonary embolism. McConnell sign of pulmonary embolism is pattern of regional right ventricular dysfunction in which apical wall motion remains normal despite hypokinesis of the free walls.

Complications

Death, pulmonary infarction, infection, cavitation, or hypertension.

Differential diagnosis

• Pulmonary embolism has a wide differential diagnosis and hence its reputation as "The Great Masquerader."

Acute massive pulmonary embolism.

Septicemia; myocardial infarction; hypovolemia; pericardial tamponade; dissection of aorta.

Subacute massive pulmonary embolism.

Pulmonary edema; pneumonia; hyperventilation; exacerbation of chronic obstructive pulmonary embolism; asthma; bronchitis; lung cancer; rib fracture; pneumothorax; costochondritis; musculoskeletal chest pain.

Chronic pulmonary embolism.

Primary pulmonary hypertension.

Chronic pulmonary embolism

Primary pulmonary hypertension.

Etiology

• >90% of pulmonary emboli originate as deep venous thrombosis of the lower extremities.

• Common causes include the following:

Surgery within past 1 month.
Medical illness (*e.g.*, myocardial infarction or stroke).
Immobility, cancer, obesity, or oral contraception.
Pregnancy or estrogen therapy.
Indwelling central venous lines.
Hypercoagulable states, which may be acquired (*e.g.*, lupus anticoagulant, anticardiolipin antibodies) or inherited (*e.g.*, antithrombin III deficiency, protein C deficiency).

Epidemiology

• At necropsy, pulmonary embolism has been found in 9%–26% of all patients; it was suspected before death in only ~16%.

• In the International Cooperative Pulmonary Embolism Registry of 2454 patients, the 3 months mortality rate was 17.5%.

• Deaths are more common in women and increase with age.

• In Medicare recipients who are 65 years of age or older men had higher fatality rates and blacks had higher fatality rates than whites.

Treatment

Diet and lifestyle

• Patients should avoid periods of sustained immobility, *e.g.*, during longhaul flights.

Pharmacological treatment

Unfractionated heparin:

• Heparin is the cornerstone of management. It accelerates the action of antithrombin III, thereby preventing an additional thrombus from forming and permitting endogenous fibrinolysis to lyse some of the clot.

• Initial therapy with oral anticoagulant and no heparin may paradoxically intensify hypercoagulability and increase the frequency of recurrent venous thromboembolism.

• If no contraindications, patients with moderate or high clinical likelihood should receive a bolus dose of unfractionated heparin (~5000–10 000 U), followed by continuous infusion initiated at dosage of 18 U/kg body weight/hour, not exceeding 1600 U/h. Usually rapidly results in a therapeutic partial thromboplastin time of 60–80 seconds. Use of a heparin nomogram facilitates proper dosing.

• Heparin-induced thrombocytopenia causes venous thrombosis more often than arterial thrombosis. Although rapid loading of warfarin used to be recommended, it may precipitate venous gangrene of the limbs. Alternatives include a heparinoid or a direct thrombin inhibitor.

Low-molecular-weight heparin:

• As effective as unfractionated heparin to treat hemodynamically stable pulmonary embolism.

Warfarin:

• Can be safely started once therapeutic partial thromboplastin time or heparin level is achieved.

• Loading dose of warfarin does not shorten the 5-day period needed to achieve anticoagulation, and an initial dose of 5 mg is often sufficient. True anticoagulation requires depletion of factor II, which takes about 5 days; at least 5 days of heparin therapy is recommended.

• The target international normalized ratio (INR) initially should be 3.0 because concomitant administration of unfractionated heparin usually prolongs heparin by an additional 0.5, thus yielding an effective INR due to warfarin alone of 2.5.

• After hospital discharge, the risk of bleeding complications and thromboembolic events can be minimized by intensive clinical monitoring. Home monitoring devices for prothrombin time have been recently approved by the FDA.

• Optimal duration of therapy is not known. Lifelong therapy is recommended in patients with recurrent pulmonary embolism. Several years of therapy is recommended for patients with deficiency of antithrombin III, protein C, or protein S. It is unclear whether patients with factor V Leiden mutation and pulmonary embolism should receive prolonged courses of anticoagulation.

Thrombolysis with anticoagulation:

• Can be life-saving in massive pulmonary thromboembolism with hemodynamic collapse.

• There appears to be 14-day window for its effective administration.

• Patients treated with anticoagulation do better than those treated with thrombolysis alone.

• Potential benefit must be weighed against risk of major hemorrhage.

Nonpharmacological treatment

Inferior vena caval filter:

• Useful when anticoagulation is contraindicated.

• Not useful in proximal deep venous thrombosis with free-floating thrombi.

• In rare cases, massive edema of legs may develop.

• Vena caval filter with anticoagulation did not reduce mortality rate compared to anticoagulation alone.

Transvenous catheter embolectomy:

• Warranted when thrombolysis is contraindicated or unsuccessful.

• High-velocity jets of saline draw the thrombus toward the catheter and pulverize the clot.

• During treatment, dobutamine or norepinephrine may be required to maintain the mean arterial pressure and ensure adequate perfusion of the right coronary artery.

Open surgical embolectomy:

• Patients with chronic cor pulmonale due to chronic thrombi may be candidates.

• Patients undergo cardiopulmonary bypass and hypothermia before incisions are made into the pulmonary arteries to remove organized thrombi.

• Pulmonary hypertension may improve, resulting in better quality of life.

• Mortality rate in selected patients in experienced centers is 5%–10%.

• Major causes of death include inability to remove sufficient thrombi at surgery, severe reperfusion-associated lung injury.

Treatment aims

To reduce morbidity of acute episode.

To prevent recurrence of pulmonary embolism or chronic pulmonary hypertension.

Prophylactic treatment

• Most deaths from pulmonary emboli are sudden or occur in patients in whom diagnosis was not suspected; significant reduction in mortality is achieved only by adequate prevention.

Physical measures: early mobilization, pneumatic calf compression, and graduated compression stockings.

Drugs: unfractionated heparin, 5000 U s.c. every 8–12 hours; low-molecular-weight heparin, 3500–5000 U once daily, depending on the type used, or low-dose warfarin.

• Percutaneous or surgical placement of inferior vena cava filter may prevent subsequent embolism in patients with recurrent pulmonary embolism despite effective anticoagulation.

Prognosis

• One-third of acute or subacute pulmonary emboli result in sudden death or are undiagnosed during life.

• Patients with untreated clinically apparent pulmonary emboli have a 30% mortality from recurrent emboli; this is reduced to 8% with effective treatment.

• Survivors of the acute or subacute episode usually have no clinical sequelae.

• Chronic pulmonary embolism carries a grave prognosis and pharmacological treatment is generally ineffective; elective thromboendarterectomy may produce long-term improvement in some patients.

• Patients who have had pulmonary emboli are at increased risk of further thromboembolic episodes when exposed to situations in which thrombosis might occur.

Follow-up and management

• Oral anticoagulant treatment and monitoring are continued for at least 3–6 months but may be continued indefinitely if underlying risk factors cannot be controlled.

General references

Carson JL, Kelley MA, Duff A, *et al.*: The clinical course of pulmonary embolism. *N Engl J Med* 1992, **326**:1240–1245.

Goldhaber SZ: Pulmonary embolism. *N Engl J Med* 1998, **339**:93–104.

Pulmonary hypertension

Diagnosis

Symptoms

• **Dyspnea:** predominant symptom with primary pulmonary hypertension. The disease often has an insidious onset in an otherwise healthy person. The disease is typically diagnosed late in its course. Dyspnea on exertion is often the earliest presenting complaint.

Easy fatiguability, exertional chest pain, syncope, near syncope, cough, hemoptysis, hoarseness (due to compression of the left recurrent laryngeal nerve by a dilated pulmonary artery).

Angina: can occur from right ventricular ischemia.

Congenital heart disease, pulmonary embolism, pulmonary fibrosis, polycythemia vera, chronic obstructive pulmonary disease (COPD): with secondary pulmonary hypertension, symptoms of the underlying disease often predominate.

Signs

• Patients with mild and moderate disease may have no signs or may develop dyspnea with minimal exertion.

Increased P2 (pulmonic component to the second heart sound): physical examination may disclose this as the disease becomes moderate.

Diastolic murmur of pulmonic regurgitation: seen in severe disease.

Evidence of right ventricular dilatation with a peristernal heave, signs of right ventricular failure (increased jugular venous distention, hepatomegaly, ascites, and pedal edema): often present with severe disease.

Right ventricular S3: may be heard.

Reduced carotid pulse.

Investigations

Chest radiography: shows enlarged central pulmonary artery and clear lung fields in primary pulmonary hypertension.

Pulmonary function tests: often normal other than a reduced diffusing capacity for carbon monoxide; may show a mild restrictive pattern.

Arterial blood gases: show hypoxemia and hypocapnea in moderate and severe disease.

ECG: shows right ventricular hypertrophy often with acute right ventricular strain (S wave in lead I and Q wave and inverted T wave in lead III).

Echocardiography: may demonstrate enlargement of pulmonary arteries with right atrial dilatation. Enlargement of the right ventricle and parodoxical septal motion are often seen. Doppler echocardiography can estimate, often quite accurately, the level of pulmonary artery systolic and mean pressures.

Nuclear ventilation–perfusion scanning: helpful to rule out chronic pulmonary embolism as a secondary cause of pulmonary hypertension.

CT: can visualize the left and right ventricular size as well as the major pulmonary arteries. CT of the lungs is useful in ruling out underlying pulmonary causes of secondary pulmonary hypertension.

Cardiac catheterization: provides precise measurement of pulmonary arterial, capillary, and venous pressures. The severity of right ventricular failure can be quantified with cardiac output measurements and wall motion can be examined. Cardiac catheterization also can identify patients with congenital or acquired intracardiac shunts.

Pulmonary angiography: best method for identifying pulmonary embolism as a secondary reason for the development of pulmonary hypertension.

Complications

Severe right heart failure with cor pulmonale: occurs in severe disease.

Progressive right ventricular failure: leads to disability and death.

Sudden death: occurs more frequently in patients with primary pulmonary hypertension.

Differential diagnosis

Mitral stenosis.

Recurrent pulmonary emboli.

Congenital cardiac defects.

Sickle cell anemia.

Collagen vascular diseases.

• Most of these, when severe, can cause secondary pulmonary hypertension.

• Differentiating primary pulmonary hypertension from secondary pulmonary hypertension is necessary. Primary pulmonary hypertension classically presents as dyspnea that is not explained by other causes (intrinsic pulmonary disease, intrinsic cardiac disease, or severe anemia).

• Deconditioning with dyspnea can sometimes mimic early primary pulmonary hypertension.

Etiology and epidemiology

• Etiology of primary pulmonary hypertension is usually idiopathic. Women outnumber men in a ratio of ~4:1.

• Postulated causes for pulmonary hypertension include autoimmune disorders due to the high frequency of antinuclear antibodies seen in some cases of pulmonary hypertension.

• Appetite suppression medication has been implicated as a possible mechanism. One of these agents was used in Europe in the late 1960s and was linked to an increase in unexplained hypertension.

• 7% of cases of pulmonary hypertension are familial, with an autosomal dominant method of transmission with variable expression.

• Secondary pulmonary hypertension is due to the underlying disease. Major causes of secondary pulmonary hypertension include massive acute pulmonary embolism or chronic recurrent embolization, COPD, living at high altitude with hypoxia, congenital heart disease, severe pulmonary vascular or parenchymal disease (including interstitial lung diseases, parasitic lung diseases, collagen vascular diseases, granulomatous lung diseases, and i.v. drug use), severe left ventricular failure, sickle cell anemia, chronic liver disease, and mitral stenosis.

Treatment

Diet and lifestyle

• Because of the link to appetite suppressant drugs, which are amphetamine-like in nature, caution is appropriate in the use of these agents for managing obesity. It is likely that there is some unknown susceptibility factor for this association. It should be stressed that this association is suspected but not proven.

Pharmacological treatment

• Pharmacological treatment for secondary pulmonary hypertension should be directed at the underlying cause.

• No satisfactory treatment exists for primary pulmonary hypertension. Logically, treatment that would decrease the pulmonary artery pressure or reduce pulmonary vascular resistance directly would be of benefit. However, most agents that achieve this also decrease cardiac output and systemic blood pressure. If pulmonary artery pressures are reduced in proportion to the decrease in cardiac output, there is little net benefit.

• General therapeutic measures include supplementing oxygen as needed to increase the arterial oxygen saturation above 85%. This permits adequate tissue oxygenation, thereby preserving functional ability and patient activity. Oxygen usually ameliorates patient dyspnea. Because hypoxia is a potent pulmonary vasoconstrictor, oxygen therapy often can result in some decrease in pulmonary artery pressures.

• Vasodilating agents have not uniformally been successful. Calcium channel blockers in high doses, *e.g.*, diltiazam, 120 mg 3 times daily, may be helpful. Unfortunately, only a minority of patients with primary pulmonary hypertension exhibit pulmonary vasoconstriction and benefit from medications that dilate pulmonary vessels. Most recently, epoprostenol has been tried and has been successful in some patients. Studies suggest that epoprostenol may decrease pulmonary pressures and increase exercise capacity. Vasodilator treatment for primary pulmonary hypertension should be started with a pulmonary artery catheter in place. Initial pharmacological evaluation can then proceed under direct monitoring of systemic and pulmonary arterial pressures, and cardiac output. The treatment of primary pulmonary hypertension remains unsatisfactory. Virtually every class of vasodilator drug has been investigated for treatment of primary pulmonary hypertension.

• Diuretic therapy may relieve dyspnea and peripheral edema but must be used cautiously so as to not markedly decrease cardiac output.

• Oral anticoagulant therapy has been advocated by some, suggesting that in situ thrombosis may occur. Some have suggested that anticoagulants increase survival; however, they do not reverse the disease.

• Heart/lung transplantation should be considered in patients with primary pulmonary hypertension. Patients who have <1 year predicted survival because of their disease are the best candidates. Recurrence of the disease has not been reported in transplantation patients.

• Inhaled nitric oxide is being studied for long-term use. It has shown promise in acute short-term management.

Treatment aims

To reduce pulmonary artery pressure and minimize hypoxemia.

Prognosis

• Prognosis for primary pulmonary hypertension is poor. Mean survival of 2–3 years from time of diagnosis is the rule. Only rare patients survive >10 years. Sudden death is not uncommon.

Follow-up and management

• Routine monitoring of arterial oxygen levels is necessary.

• Patients should be monitored for disease progression.

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