5th Edition

CURRENT
Diagnosis & Treatment

Family
Medicine

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Gallstone Pancreatitis

ESSENTIALS OF DIAGNOSIS

▶ RUQ or epigastric pain.
▶ Elevated serum amylase and lipase.
▶ Ultrasound evidence of gallstones.

Gallstones small enough to pass through the biliary tree may enter the pancreatic duct and potentially obstruct at the level of the ampulla of Vater. These stones will then cause obstruction of the pancreatic ductal system, resulting in pancreatitis. Gallstones are associated with approximately 45–50% of all cases of pancreatitis in the United States.

Patients presenting with pancreatitis typically have varying degrees of abdominal pain, usually located in the epigastrium or RUQ. The pain may radiate to the back or shoulders. Nausea and vomiting are common. Laboratory studies will reveal elevation of lipase and (occasionally) amylase. If gallstones remain in the biliary tree, then liver transaminases and bilirubin may also be elevated. Although ultrasound is useful to confirm presence of gallstones, computed tomography (CT) scanning is useful in delineating the severity of pancreatitis.

The treatment of gallstone pancreatitis is eventual cholecystectomy. As the gallbladder is the source of the stones, cholecystectomy will prevent subsequent episodes of pancreatitis. Cholecystectomy should not be attempted until the resolution of pancreatitis. Treatment for pancreatitis involves bowel rest with intravenous hydration. Severe cases of pancreatitis may require intensive care unit admission with cardiovascular and respiratory support. Regardless of the patient's condition, cholecystectomy should be postponed until after the pancreatitis has resolved. It has been suggested that morbidity and mortality are improved if these patients undergo ERCP within 2 days of onset of symptoms. ERCP may be able to remove an impacted stone and thus allow for pancreatic decompression. This approach is generally considered in patients with moderate or severe pancreatitis.

The presence or absence of a persistent bile duct stone should be determined prior to proceeding with cholecystectomy. In most circumstances, normalization of serum lipase, amylase, and liver function tests (if originally elevated) occurs rapidly. In these circumstances, no imaging of the biliary tree is required because of the low probability of a persistent bile duct stone. However, patients with persistent abnormalities of their liver functions, amylase, or lipase should be evaluated for the presence of common bile duct stones. Biliary imaging may be obtained by means of intraoperative cholangiography at the time of cholecystectomy, perioperative ERCP, or magnetic resonance cholangiopancreatography

(MRCP). MRCP is the least invasive modality but is only diagnostic. ERCP allows for both visualization and extraction of stones of diameter ≤1.5 cm. ERCP may be used to extract common bile duct stones either antecedent or subsequent to cholecystectomy. Common bile duct stones not amenable to endoscopic removal are removed operatively by performing a common bile duct exploration.

The overall long-term outcome of patients is related to the severity of the pancreatitis. Localized morbidity includes pancreatic necrosis, splenic vein thrombosis with gastric varices, hemorrhagic pancreatitis, and pancreatic abscess formation. Systemic morbidity can result in multisystem organ failure or even death.

Behrns KE, Ashley SW, Hunter JG, et al. Early ERCP for gallstone pancreatitis: for whom and when? *J Gastrointest Surg.* 2008;12:629–633. [PMID: 17846851]

Kaw M, Al-Antably Y, Kaw P. Management of gallstone pancreatitis: cholecystectomy, or ERCP and endoscopic sphincterotomy. *Gastroinest Endosc.* 2002;56:61–65. [PMID: 12085036]

Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev.* 2012;16:CD009779. [PMID: 22592743]

Cholangitis

ESSENTIALS OF DIAGNOSIS

▶ Persistent RUQ pain.
▶ Jaundice.
▶ Fever.
▶ Hypotension, mental status changes (acute suppurative cholangitis).

Cholangitis is defined as inflammation of the biliary system. It is most commonly caused by an impacted gallstone at the ampulla of Vater preventing bile drainage into the duodenum, although other etiologies such as extrinsic compression from an adjacent mass, inflammatory process, or a primary tumor of the ampulla, duodenum, or bile duct should also be considered. Cholangitis is considered a medical emergency.

Patients with cholangitis may present with Charcot's triad (fever, RUQ pain, and jaundice) or with Reynold's pentad (the addition of hypotension or mental status changes). Laboratory studies will show hyperbilirubinemia and leukocytosis. Ultrasound will likely show biliary ductal dilatation.

With clinical suspicion of cholangitis, patients should be immediately resuscitated and given broad-spectrum antibiotics. Biliary decompression should be urgently performed by ERCP. If ERCP fails to resolve the obstruction or is not

available, percutaneous transhepatic cholangiography (PTC) with drainage may be performed. In the presence of stones, once biliary decompression has been performed, cholecystectomy should be performed electively following resolution of the cholangitis. In rare circumstances in which percutaneous or endoscopic biliary drainage is not possible, urgent cholecystectomy with common bile duct exploration should be performed.

The mortality associated with cholangitis varies widely and is related to the underlying etiology of the cholangitis. Cholangitis secondary to stones is associated with a low overall mortality provided the patient can be successfully supported through the infectious period. Cholangitis related to an underlying periampullary malignancy requires careful oncologic consideration prior to surgical intervention. This may require a more involved oncologic resection (eg, a pancreaticoduodenectomy or extrahepatic biliary resection) or palliative care depending on the extent of the malignancy. In the event of an unresectable periampullary tumor, a biliary bypass (hepaticojejunostomy) may be considered. Most periampullary cancers are associated with very poor 5-year survival even with complete extirpation of the tumor.

Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. *N Engl J Med.* 1992;326:1582–1586. [PMID: 1584258]

Lee JG. Diagnosis and management of acute cholangitis. *Nat Rev Gastroenterol Hepatol.* 2009;6(9):533–541. [PMID: 19652653]

Sugiyama M, Atomi Y. Treatment of acute cholangitis due to choledocholithiasis in elderly and younger patients. *Arch Surg.* 1997;132:1129–1133. [PMID: 9336514]

Biliary Dyskinesia

A small group of patients will present with RUQ abdominal pain and symptoms that follow the pattern of biliary disease but will have essentially negative imaging for biliary pathology. One key factor in ascertaining whether the gallbladder is contributing to their pain would be to perform a HIDA scan with cholecystokinin (CCK) injection. Likewise, measurement of gallbladder ejection fraction (EF) during this scan can further identify patients with biliary pathology. EFs of <35% are considered pathophysiologic and warrant evaluation for cholecystectomy. Reproduction of pain with CCK injection is diagnostic for biliary dyskinesia, and these patients benefit from referral for cholecystectomy. Laparoscopic cholecystectomy has been reported to alleviate pain in ≤94% of patients with biliary dyskinesia. Patients with the highest success rate were those presenting with complaints of nausea or pain or with EF <15% by HIDA scan. Patients with vague abdominal complaints should be cautioned that laparoscopic cholecystectomy is not guaranteed to alleviate their symptoms, and the decision to proceed with surgical intervention should be made carefully on a case-by-case basis.

Bingener J, Sirinek KR, Schwesinger WH, et al. Laparoscopic cholecystectomy for biliary dyskinesia. *Surg Endosc.* 2004;18: 802–806. [PMID: 15054652]

Yost F, Murayama K. Cholecystectomy is an effective treatment for biliary dyskinesia. *Am J Surg.* 1999;178(6):462–465. [PMID: 10670853]

BILIARY MALIGNANCIES

Gallbladder Polyps

Gallbladder polyps are present in ~5% of the population and are usually found incidentally during abdominal ultrasonography. The different types of polyps include cholesterolosis, adenomyomatosis, hyperplastic cholecystosis, and adenocarcinomatosis. The goal of surgical management is to identify which polyps are cancerous (adenocarcinoma) or at risk of developing cancer (adenomyomatosis) and select these patients for cholecystectomy.

Unfortunately, short of cholecystectomy, there is currently no way to distinguish among the different types of gallbladder polyps. With the relative safety of laparoscopic cholecystectomy, some advocate surgery immediately after discovering polyps. Patients who have polyps with gallstones or are age >50 years should be referred for cholecystectomy. Further imaging techniques, including endoscopic ultrasound (EUS), have been advocated for small polyps. Recent recommendations include removing polyps of diameter ≥6 mm because of an increased likelihood of malignancy. If cancer is present in the surgical specimen, the depth of invasion dictates the next course of therapy.

Gallahan WC, Conway JD. Diagnosis and management of gallbladder polyps. *Gastroenterol Clin North Am.* 2010;39(2): 359–367. [PMID: 20478491]

Gallbladder Cancer

Patients with gallbladder cancer have presentations similar to those with symptomatic cholelithiasis or chronic cholecystitis. Presentation is often late, and with advanced disease, systemic complaints such as gradual weight loss and loss of appetite also appear. Since presentation is often assumed to be related to gallstone disease, ultrasound is usually the initial diagnostic modality used. Ultrasound findings of a mass >1 cm, calcified gallbladder wall, discontinuity of gallbladder wall layers, and loss of interface between the gallbladder wall and the liver should raise suspicion of gallbladder cancer. CT is useful in these circumstances to delineate anatomic structures for resectability, as well as evidence of metastatic disease.

The presence of paraaortic or peripancreatic lymphadenopathy is deemed unresectable disease. This can be confirmed with EUS with biopsies. Cancers that are limited to the mucosa or muscular layer of the gallbladder can be

treated with cholecystectomy with negative margins alone. Tumors that invade the pericholecystic connective tissue require resection of the gallbladder fossa with en bloc cholecystectomy. Tumors that invade the liver require formal resection of the involved segments. Unfortunately, 15–50% of tumors that penetrate the muscular wall of the gallbladder have nodal disease that will render them unresectable. Gallbladder cancer may also be found incidentally in cholecystectomy specimens. If it is invasive, additional resection of involved hepatic margins will be necessary. The 5-year survival of early tumors (those confined to the muscular or mucosal layer) is excellent (90–100%). The survival for more advanced tumors is measured in terms of weeks or months.

Bartlett DL, Fong Y, Fortner JG, et al. Long-term results after resection for gallbladder cancer: implications for staging and management. *Ann Surg.* 1996;224:639–646. [PMID: 8916879]

Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg.* 2000;232:557–569. [PMID: 10998654]

Choledochal Cyst

Classically, a choledochal cyst is described as a palpable RUQ mass in a young female with jaundice. Most choledochal cysts are described in Asian populations but are increasingly seen in the United States, males, and older patients. Choledochal cysts are classified by their anatomic location; most involve solitary fusiform dilatation of the extrahepatic biliary tree. Their presentation in Western series is similar to that of symptomatic cholelithiasis. They can be easily seen on ultrasound—provided the ultrasonographer evaluates the biliary tree in addition to the gallbladder.

Choledochal cysts are associated with a 70-fold increased incidence of cholangiocarcinoma, so surgical resection is indicated when discovered. Operative treatment involves resection of the entire extrahepatic biliary tree, cholecystectomy, and reconstruction with a Roux-en-Y hepaticojejunostomy. Surgical resection is considered curative; Edil et al. (2008) reported no subsequent malignancy over 30 years in patients without cancer at the time of cyst excision.

Edil BH, Cameron JL, Reddy S, et al. Choledochal cyst disease in children and adults: a 30-year single institution experience. *J Am Coll Surg.* 2008;206:1000–1005. [PMID: 18471743]

Cholangiocarcinoma

For various reasons, cholangiocarcinomas along with other RUQ malignancies are associated with very poor survival: (1) these lesions often present late and are not amenable to resection; (2) their biological activity is not well understood, and systemic therapy offers little benefit; and (3) operative resection is technically difficult, and patients need to be seen in specialized centers.

The vast majority of cholangiocarcinomas present with jaundice, sometimes in the setting of cholangitis. Ultrasound will often show a dilated proximal biliary tree. ERCP and EUS are useful to delineate the tumor. Preoperative endoscopic brushings are often nondiagnostic and should not be aggressively pursued in patients with resectable disease on cross-sectional imaging. While most proximal cholangiocarcinomas (70%) are not amenable to resection, approximately half of distal tumors may be resected. Resection involves pancreaticoduodenectomy for distal tumors and extrahepatic biliary resection with Roux-en-Y hepaticojejunostomy for proximal disease. The 5-year survival rate remains poor even after complete resection (20–25%). For patients with unresectable disease, survival is again measured in weeks or months.

Fong Y, Blumgart LH, Lin E, et al. Outcome of treatment for distal bile duct cancer. *Br J Surg.* 1996;83:1712–1715. [PMID: 9038548]

Jarnigan WR, Fong Y, DeMatteo RP, et al. Staging, resectability and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg.* 2001;234:507–517. [PMID: 11573044]

LeFemina J, Jarnagin WR. Surgical management of proximal bile duct cancers. *Langenbecks Arch Surg.* 2012;397(6):869–879. [PMID: 22391776]

▼ LIVER DISEASE

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VIRAL HEPATITIS

ESSENTIALS OF DIAGNOSIS

▶ Variable prodromal signs and symptoms.

▶ Positive specific viral hepatitis tests.

▶ Elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Acute viral hepatitis is a worldwide problem, and in the United States alone, there are probably between 200,000 and 700,000 cases per year according to the Centers for Disease Control and Prevention (CDC). Over 32% of cases are caused by hepatitis A virus (HAV), 43% by hepatitis B virus (HBV), 21% by hepatitis C virus (HCV), and the remainder are not identified. Although few deaths (~250) due to acute hepatitis are reported annually, considerable morbidity can result from chronic hepatitis caused by HBV and HCV infections, and mortality from complications can be pronounced for years to come.

Hepatitis A

▶ General Considerations

HAV, first identified in 1973, is the prototype for the former diagnosis of *infectious hepatitis*. Over the past several decades, the incidence of HAV infection has varied considerably, and a high number of cases have gone unreported. HAV is a very small viral particle that is its own unique genus (*Hepatovirus*).

Most individuals infected worldwide are children. In general, there are four patterns of HAV distribution (high, moderate, low, and very low), which roughly correspond to differing socioeconomic and hygienic conditions. Countries with poor sanitation have the highest rates of infection. Most children age <9 years in these countries manifest evidence of HAV infection. Countries with moderate rates of infection have the highest incidence in later childhood; food- and waterborne outbreaks are more common. In countries with low endemicity, the peak age of infection is likely to be at early adulthood, and in very low endemic countries, outbreaks are uncommon.

Hepatitis A is usually transmitted by ingestion of contaminated fecal material of an infected person by a susceptible individual. Contaminated food or water can be the source of infection, but occasionally infection can occur by contamination of different types of raw shellfish from areas contaminated by sewage. The virus can survive for 3–10 months in water. Other cases of infection by blood exposures have been reported but are less common. The incubation period for HAV averages 30 days, with a range of 15–50 days.

In countries of low endemicity, persons at greatest risk for infection include travelers to intermediate and high-HAV-endemic countries, men who have sex with men (MSMs), injection or noninjection drug users, persons with occupational risks of infection, household members and other close personal contacts of adopted children newly arriving from the countries mentioned, persons with clotting factor disorders, persons with chronic liver disease, including those who have received transplants, and persons who have direct contact with persons infected with hepatitis A. In areas of high endemicity, all young children are at increased risk.

▶ Prevention

Currently in the United States, the CDC recommends that certain populations at increased risk be considered for preexposure vaccination; these include the groups listed earlier. In addition, the CDC now recommends universal immunization for all children age ≥1 year. The immunization schedule consists of three doses for children and adolescents and two for adults. In groups with the potential for high risk of exposure, including any adult age >40 years, prevaccination testing for prior exposure may be cost effective. The appropriate test is the total anti-HAV. Travelers age <40 years who receive the vaccine may assume to be protected after receiving the first dose, although the second dose is desired for long-term protection. For certain travelers (older adults and those with underlying medical conditions), immunoglobulin (Ig) may be given in a different site for additional protection within 2 weeks of travel. A combination vaccine with HBV is available for persons age >18 years who are immunocompetent and is used on the same three-dose schedule as HBV.

Ig or hepatitis A vaccine (if previously unvaccinated) may also be used for postexposure prophylaxis in healthy patients between 12 months and 40 years of age, if given within 14 days, and would most often be used for household or intimate contacts of an infected person, in some institutional settings, or if a common source is identified. For persons with chronic illness or those age <12 months or >40 years, Ig is preferred.

▶ Clinical Findings

A. Symptoms and Signs

The symptoms and signs of acute viral hepatitis are quite similar regardless of type and are difficult to distinguish on the basis of clinical findings. The prodrome for viral hepatitis is variable and may be manifested by anorexia, including changes in olfaction and taste, as well as nausea and vomiting, fatigue, malaise, myalgias, headache, photophobia, pharyngitis, cough, coryza, and fever. Dark urine and clay-colored stools may be noticed 1–5 days before jaundice.

Clinical jaundice varies considerably and may range from an anicteric state to rare hepatic coma. In acute HAV infection, jaundice is usually more pronounced in older age groups (ie, 70–80% in those age 14 years) and rare in children age <6 years (<10%). Weight loss may also be present, as well as an enlarged liver (70%) and splenomegaly (20%). Spider angiomata may be present without acute liver failure. Patients may also report a loss of desire for cigarette smoking or alcohol.

B. Laboratory Findings

Usually, the onset of symptoms coincides with the first evidence of abnormal laboratory values. Acute elevations of ALT and AST are seen, with levels as high as 4000 units or more in some patients. The ALT level is usually higher than the AST. When the bilirubin level is >2.5, jaundice may be obvious. Bilirubin levels may go from 5 to 20, usually with an equal elevation of conjugated and unconjugated forms. The prothrombin time is usually normal. If significantly elevated, it may signal a poor prognosis. The complete blood count may demonstrate a relative neutropenia, lymphopenia, or atypical lymphocytosis. Urobilinogen may be present in urine in the late preicteric stage.

Serum IgM antibody (anti-HAV) is present in the acute phase and usually disappears within 3 months, although

occasionally it persists longer. IgG anti-HAV is used to detect previous exposure and persists for the lifetime of the patient. The more commonly available test for IgG anti-HAV is the total anti-HAV.

▶ Treatment

Treatment for the most part is symptomatic, with many clinicians prohibiting only alcohol during the acute illness phase. Most patients can be treated at home.

▶ Prognosis

In the vast majority of patients with HAV, the disease resolves uneventfully within 3–6 months. Rarely, fulminant hepatitis may develop, with acute liver failure and high mortality rates. Rare cases of cholestatic hepatitis, with persistent bilirubin elevations, have also been reported. Some patients develop relapsing hepatitis, in which HAV is reactivated and shed in the stool. Affected patients demonstrate liver function test abnormalities, but virtually all recover completely. HAV does not progress to chronic hepatitis.

Hepatitis B

▶ General Considerations

HBV is a double-shelled DNA virus. The outer shell contains the hepatitis B surface (HBsAg). The inner core contains several other particles, including hepatitis core antigen (HBcAg) and hepatitis B e antigen (HBeAg). These antigens and their subsequent antibodies are described in more detail later.

Worldwide, >400 million people are infected with HBV, but the distribution is quite varied. More than 45% of the global population live in areas of high incidence (infections in >8% of population). There, the lifetime risk of infection is >60%, and early childhood infections are very common. Intermediate-risk areas (infections in 2–7% of the population) represent 43% of the global population. The lifetime risk of infection in these areas is between 20% and 60%, and infections occur in various age groups. In low-risk areas (infections in <2%), which represent ~12% of the global population, the lifetime risk of infection is <20% and is usually limited to specific adult risk groups.

In the United States, HBV is normally a disease of young adults. The largest numbers of cases are reported in adults age 20–39 years, but many cases in younger age groups may be asymptomatic and go unreported. Of the specific risk groups in the United States, >50% in recent studies are those with sexual risk factors (more than one sex partner in the past 6 months, sexual relations with an infected person, or MSM transmission). Over 15% had a history of injection drug use, and 4% had other risk factors such as a household contact with HBV or a healthcare exposure. The mode of transmission can thus be sexual, parenteral, or perinatal, through contact of the infant's mucous membranes with maternal infected blood at delivery.

Body fluids with the highest degree of concentration of HBV are blood, serum, and wound exudates. Moderate concentrations are found in semen, vaginal fluid, and saliva, and low or nondetectable amounts are found in urine, feces, sweat, tears, or breast milk. Saliva can be implicated in transmission through bites, but not by kissing.

The average incubation period for HBV is between 60 and 90 days, with a range of 45–180 days. Although the incidence of jaundice increases with age (<10% of children <5 years old demonstrate icterus compared with 30–50% of those age >35 years), the likelihood of chronic infection with HBV is greater when infection is contracted at a younger age. Between 30% and 90% of all children who contract HBV before the age of 5 years develop chronic disease, compared with 2–10% of those age >35 years.

▶ Prevention

Current immunization recommendations in the United States call for routine immunization of all infants, children, adolescents, and adults in high-risk groups, including all diabetic patients age 19–58 years and all patients with chronic liver disease, including those with chronic hepatitis C and/or significantly elevated liver enzymes. Acknowledgment of a specific risk factor is not a requirement for immunizations. These recommendations include immunizing all children at birth within 24 hours if birth weight is ≥2000 g and at 1 and 6 months. Additionally, all high-risk groups should be screened, as well as all pregnant women. Prevaccination testing of patients in low-risk groups is probably not necessary, but in high-risk groups, this may be cost effective. As illustrated in the first test scenario of Table 33–2, a negative HBsAg titer and a negative anti-HBs titer are evidence of susceptibility to HBV.

The vaccine contains components of HBsAg. Pretesting with anti-HB core antibody (anti-HBc) is probably the single best test, because it would identify those who are infected and those who have been exposed. Posttesting for vaccine is seldom recommended, except for individuals who may have difficulty mounting an immune response (eg, immunocompromised patients). In these patients, the hepatitis B surface antibody (anti-HBs) would be the appropriate test. Some authorities recommend revaccinating high-risk individuals if titer levels have fallen below 10 IU/L after 5–10 years or if they have failed to mount an appropriate immune response with the standard dosing and schedule.

Children born to women of unknown hepatitis B status should receive a first dose of hepatitis B vaccine within 12 hours of birth as well as hepatitis B immune globulin (HBIG) and HBIG within 7 days for infants ≥2000 g if maternal blood is positive. Repeat testing of all infants born to HBV-infected mothers should be performed at 9–18 months with HBsAg

Table 33–2. Interpretation of the hepatitis B panel.

Tests	Results	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune because of natural factors
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune because of hepatitis B vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Four interpretations possible[a]

[a]May be (1) recovering from acute hepatitis B virus infection, (2) distantly immune and the test is not sensitive enough to detect very low levels of anti-HBs in serum, (3) susceptible with a false-positive anti-HB; or (4) an undetectable level of HBsAg is present in the serum and the person is actually a carrier.

and anti-HBs. Infants born to HBV-infected mothers should receive both the first dose of hepatitis B vaccine at birth as well as 0.5 mL of HBIG in separate sites within 12 hours after birth. Recommendations for postexposure prophylaxis of HBV can be reviewed in the current CDC recommendations.

▶ **Clinical Findings**

Acute infection may range from an asymptomatic infection to cholestatic hepatitis to fulminant hepatic failure. HBsAg and other markers usually become positive about 6 weeks after infection and remain positive into the clinical signs of illness. Other biochemical abnormalities begin to show abnormalities in the prodromal phase and may persist for several months, even with a resolving disease process. Anti-HB core IgM becomes positive early, with onset of symptoms, and both anti-HB core IgM and anti-HB core IgG may persist for many months or years. Anti-HBs is the last antibody to appear and may indicate resolving infection. The presence of HBeAg indicates active viral replication and increased infectivity (Figure 33–1). Liver function tests should be obtained early in the course of infection, and

evidence of prolonged prothrombin time (international normalized ratio >1.5) should raise concern for hepatic failure. Patients who remain chronically infected may demonstrate HBsAg and HBeAg for at least 6 months, with a usual trend in liver function tests toward normal levels, although results may remain persistently elevated (Figure 33–2). Extrahepatic manifestations of HBV infection may occur and include serum sickness, polyarteritis nodosa, and membranoproliferative glomerulonephritis.

▶ **Complications**

Complications of chronic infection may include progression to cirrhosis and hepatocellular carcinoma (HCC). Patients with active viral replication are at highest risk of chronic disease, with 15–20% developing progressive disease over a 5-year period. Continued positivity for HBeAg is associated with an increased risk of HCC. Most patients who are chronically infected remain HBsAg positive for their lifetime. There is no general agreement concerning the appropriate screening for patients with chronic infection for HCC. Guidance statements recommend screening all patients with cirrhosis with ultrasonography with or without α-fetoprotein every 6 months.

▶ **Treatment**

Treatment for chronic disease depends on evidence of viral activity, HBeAg status, human immunodeficiency virus (HIV) and HCV comorbidity, histologic evidence of liver injury, and elevated liver function tests. Currently approved treatment modalities include interferon-alfa, pegylated interferon, and nucleoside(tide) analogs, such as lamivudine, telbivudine, adefovir, tenofovir disproxil, tenofovir alfenamide, and entecavir. Other new antiviral agents are currently being tested. Sensitive tests for determination of response to therapy, such as covalently closed circular DNA, may be more readily available in the future, although most patients will receive treatment indefinitely.

Hepatitis C
▶ **General Considerations**

HCV has become the most common bloodborne infection as well as the leading cause of chronic liver disease and, subsequently, liver transplantation in the United States. Worldwide, >180 million people are infected, but the infection rates vary considerably. In the United States, it is estimated that approximately 4 million people may be infected with HCV; it is the main cause of death from liver disease. The responsible virus is an RNA virus of the Flaviviridae family. Six major genotypes, numbered 1 through 6, are known, with additional subtypes. There are varying distributions of these genotypes, and they may affect the progression of disease and the response to treatment regimens.
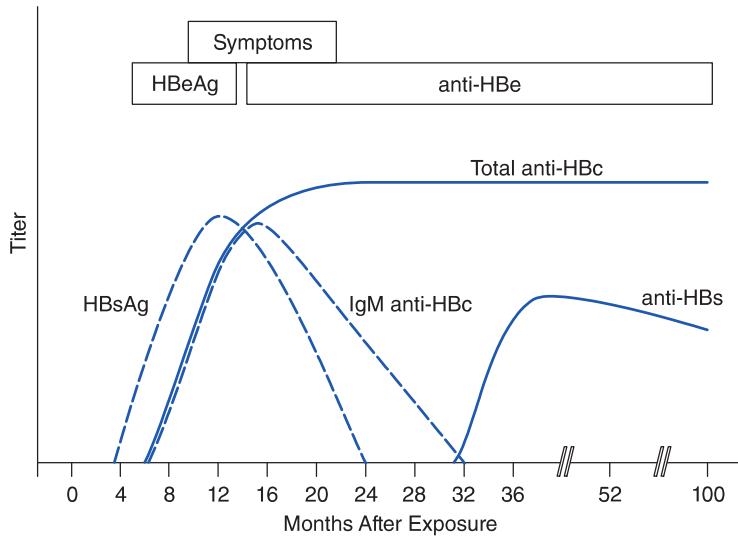
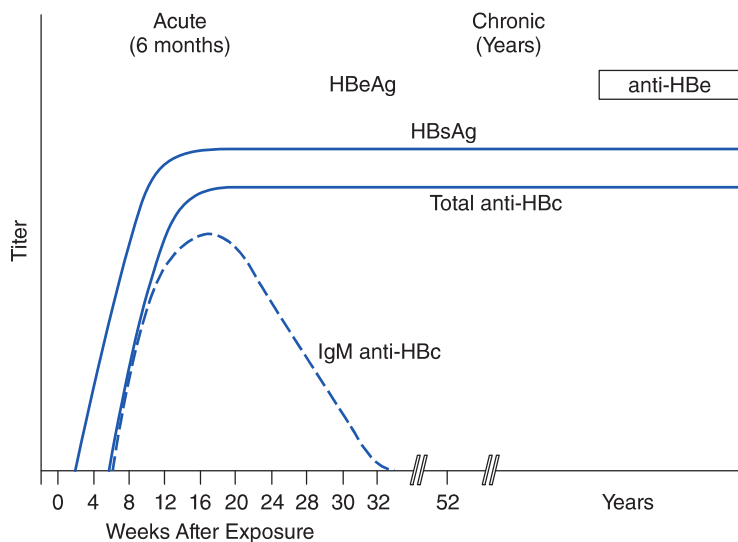▲ **Figure 33–1.** Acute hepatitis B virus infection with recovery.

Hepatitis C is spread primarily through percutaneous exposure to blood. Since 1992, all donated blood has been screened for HCV. Injection drug use is responsible for >50% of new cases. Within 1–3 months after a first incident of needle sharing, 50–60% of intravenous drug users are infected. Other risk factors include use of intranasal cocaine, hemodialysis, tattooing (debatable), and vertical transmission, which is rare. Breastfeeding carries a low risk of transmission. Sexual transmission is uncertain but is probably 1–3% over the lifetime of a monogamous couple, one of whom is infected. Healthcare workers are at particular risk following a percutaneous exposure (1.8% average incidence).

One-time screening of all individuals born between 1945 and 1965 has been recommended by the CDC, along with screening of patients with known risk factors.

▶ **Prevention**

No immunizations are currently available for HCV infections. Prevention consists mainly of reduction of risk factors,

▲ **Figure 33–2.** Progression to chronic hepatitis B virus infection.

including screening of blood and blood products, caution to prevent percutaneous injuries, and reduction in intravenous drug use.

▶ Clinical Findings

A. Symptoms and Signs

1. Acute hepatitis—The incubation period for HCV varies between 2 and 26 weeks, but most commonly is 6–7 weeks. Most patients with HCV are asymptomatic at the time of infection. However, >20% of all recognized cases of acute hepatitis in the United States are caused by HCV, and as many as 30% of adults who are infected may present with jaundice. Acute, fulminant hepatic failure is rare.

2. Chronic hepatitis—In contrast to HAV and HBV, most people infected with HCV (85%) develop a chronic infection. The incidence of significant liver disease is 20–30% for cirrhosis and 4% for liver failure; >1–4% of patients with chronic infection develop HCC annually, or 11–19% over 4–11 years in one study. It appears that certain risk factors increase the likelihood of progression to serious disease. These include increased alcohol intake, age >40 years, HIV coinfection, and possibly male gender and other liver coinfections.

Extrahepatic manifestations of chronic infection are fairly common and are similar to those of HBV, including autoimmune conditions and renal conditions such as membranous glomerulonephritis.

B. Laboratory Findings

Patients in a high-risk category for HCV should be tested with both an approved HCV antibody test such as the Ora-Quick HCV Rapid Antibody test or other approved tests and a confirmatory test by a sensitive HCV RNA test if positive. All patients with HCV infection should have a quantitative HCV-RNA test as well as HCV genotyping prior to therapy in order to select the recommended treatment regimen and predict a therapeutic response, as well as duration of therapy. Evaluation of the stage of fibrosis, for concomitant infection with HIV or hepatitis B or A, and for potential for renal disease and pregnancy is also important.

▶ Treatment

Treatment for both acute and chronic HCV has undergone major strides in recent years. A recent study documents the conversion of a significant number of patients to negative serology when treated in the acute phase of infection; treatment is now recommended for all patients with chronic HCV infection with few exceptions. Virologic cure can be expected in most patients. The development of direct-acting antivirals, such as NS3 protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors, has dramatically changed the response rate to therapy in all of the genotypes. It is

important to check guidelines for the latest recommendation for specific subtypes of HCV disease. Many of these regimens are interferon and ribavirin free, which greatly simplifies the therapy and decreases the incidence of therapeutic complications. Therapy is usually given for 12 weeks, and sustained viral load can be expected in at least 95% of patients at this time. Other new treatments are currently under investigation.

It is important to immunize patients with chronic HCV infection for HAV, because the incidence of fulminant hepatitis A has been shown to be significantly increased in this population. Patients infected with HCV should also abstain from alcohol. It has also been recommended that HCV-infected individuals be vaccinated for HBV, owing to the poor prognosis of coinfected individuals. Chronic hepatitis C can also progress to cirrhosis and HCC, and appropriate screening measures as discussed in the section on hepatitis B apply to hepatitis C–infected patients as well.

Other Types of Infectious Hepatitis

Over 97% of cases of viral hepatitis in the United States are either A, B, or C. Other types of viral hepatitis occur much less frequently, although worldwide, they may be more important.

Hepatitis D

Hepatitis D virus (HDV) can replicate only in the presence of HBV infection. HDV infection can occur either as a coinfection with HBV or as a superinfection in a chronically infected individual with HBV. Although coinfection can produce more severe acute disease, a superinfection poses the risk of more significant chronic disease, with 70–80% of patients developing cirrhosis. The mode of transmission is most commonly percutaneous. The only tests commercially available in the United States are total (IgG and IgM)–anti-HDV. Prevention of HDV depends on prevention of HBV. There are no products currently available to prevent HDV infection in patients infected with HBV.

Hepatitis E

Hepatitis E virus (HEV) is the most common cause of enterically transmitted non-A, non-B hepatitis. Acute HEV infection is similar to other forms of viral hepatitis; no chronic form is known. Severity of illness increases with age, and for reasons that are unclear, case fatality rates are particularly high in pregnant women. Most cases of HEV reported in the United States have occurred in travelers returning from areas of high endemicity. In certain areas of the world (Mexico, North Africa, the Middle East, and Asia), epidemics of HEV may be common. Prevention includes avoidance of drinking water and other beverages of unknown purity, uncooked shellfish, and uncooked vegetables and fruits. Vaccines for hepatitis E are not universally available.

Acute Hepatitis: A Cost-Effective Approach

Because the vast majority of viral hepatitis cases are caused by HAV, HBV, or HCV, tests to determine the precise etiology are necessary for appropriate primary and secondary prevention for the patient, as well as potential for therapy. If these tests fail to indicate a diagnosis, the etiology may be due to less frequent causes of viral hepatitis such as Epstein-Barr virus, in which jaundice rarely accompanies infectious mononucleosis; cytomegalovirus or herpesvirus in immuno-compromised patients; or other nonviral etiologies, such as alcoholic hepatitis, drug toxicity, Wilson disease, or an auto-immune hepatitis.

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Websites

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American Liver Foundation. Liver Update: Function and Disease (excellent survey of issues pertaining to hepatitis). http://www.liverfoundation.org

Centers for Disease Control and Prevention: Hepatitis informa-tion (references for immunization and testing, as well as patient information in several languages). http://www.cdc.gov/hepatitis/

ALCOHOLIC LIVER DISEASE

ESSENTIALS OF DIAGNOSIS

▶ History of alcohol use.
▶ Mildly elevated serum ALT and AST.
▶ Variable clinical signs (may include jaundice, hepatomegaly).

▶ General Considerations

Alcoholic liver disease (ALD) includes several different dis-ease entities, spanning a large clinical spectrum. These dis-eases range from the syndrome of acute fatty liver to severe liver damage as manifested by cirrhosis. *Fatty liver* is usually asymptomatic except for occasional hepatomegaly and is the histologic result of excessive use of alcohol over a several-day period. In *perivenular fibrosis*, fibrous tissue is deposited in the central areas of the liver, particularly the central veins; this indicates that the individual may then rapidly progress to more severe forms of liver disease. Patients can progress from this stage directly to cirrhosis. *Alcoholic hepatitis* is a condition in which necrosis of hepatic cells occurs as part of an inflam-matory response, which includes polymorphonuclear cells, along with evidence of fibrosis. *Cirrhosis* may result from con-tinued progression of disease from alcoholic hepatitis or may occur without evidence of prior alcoholic hepatitis. Cirrhosis is characterized by distortion of the liver structure, with bands of connective tissue forming between portal and central zones. Changes in hepatic blood circulation may also occur, resulting in portal hypertension. Additionally, evidence of abnormal fat metabolism, inflammation, and cholestasis may be seen. Pro-gression to HCC may also occur, although the exact risk of cirrhosis itself in the progression to HCC is not clear.

It is known that women are more likely than men to develop severe end-stage ALD, although the reasons for this phenomenon are only now being clarified. There may be additional genetic factors, most notably in specific enzyme systems, such as the metabolism of tumor necrosis factor (TNF) and alcohol-metabolizing systems, which affect the development of disease. Concomitant diseases, such as HCV infection, obesity, metabolic syndrome, and malnutrition, may also be additional risk factors.

▶ Clinical Findings

A. Symptoms and Signs

A history of drinking alcohol in excess of >3 drinks/day for men and >2 drinks/day for women is related to an increased

risk for ALD. Numerous questionnaires have been designed for detection of excessive drinking, but the CAGE questionnaire (**c**ut down, **a**nnoyed by criticism, **g**uilty about drinking, **e**ye-opener drinks) and the Alcohol Use Disorders Inventory Test (AUDIT) are probably the most useful.

Clinical findings may be limited at this stage to occasional hepatomegaly. Patients with alcoholic hepatitis may present with classic signs and symptoms of acute hepatitis, including weight loss, anorexia, fatigue, nausea, and vomiting. Hepatomegaly may be evident, as well as other signs of more advanced disease, such as cirrhosis, because the development of cirrhosis may occur concomitant with a new episode of alcoholic hepatitis. These signs include jaundice, splenomegaly, ascites, spider angiomas, and signs of other organ damage secondary to alcoholism (eg, dementia, cardiomyopathy, or peripheral neuropathy).

B. Laboratory Findings

Various commercially available laboratory tests have been used to detect excessive alcohol intake in the early stages. The sensitivity and specificity of these tests vary. Liver function tests for elevations of AST, ALT, and γ-glutamyl transferase are frequently used. Elevation of mean corpuscular volume (MCV) has also been noted in patients with early-stage disease.

Transaminase levels are usually only mildly elevated in pure alcoholic hepatitis unless other disease processes, such as concomitant viral hepatitis, or acetaminophen ingestion, are present; AST is usually elevated to ≤200 IU/L, and AST to ≤500 IU/L. An AST/ALT ratio >1.5 is usually present. Elevated prothrombin time and bilirubin levels have a significant negative prognostic indication. *The presence of jaundice may have special significance in any actively drinking person and should be carefully evaluated.* Several instruments have been used for evaluation of severity, but the most common is the Maddrey discriminant function (MDF) or the Model for End-State Liver Disease (MELD) score. An MDF score >32 or a MELD score of >2 is indicative of severe disease.

▶ Treatment

Abstinence from alcohol is essential and is probably the most important of all therapies. Recovery from the acute episode is associated with an 80% 7-year survival rate in patients who can abstain from alcohol versus 50% survival in those who continue drinking. The use of naltrexone or acamprosate in conjunction with counseling and support groups to prevent recidivism should be considered.

Initial treatment of the acutely ill patient centers on ensuring adequate volume replacement, with concern for the ability to handle normal saline. Diuretics should be used cautiously. Patients should be assessed for protein-calorie malnutrition and vitamin and mineral deficiencies. Adequate nutrition should be given to patients with severe disease,

parenterally if necessary. There is no indication that avoidance of protein is helpful in patients with encephalopathy. Broad-spectrum antibiotics should be considered early in the treatment course. Many patients develop spontaneous peritonitis, pneumonia, or cellulitis, which should be treated aggressively. Corticosteroids have been suggested as beneficial, but considerable debate still ensues as to whether there is any benefit to survival, although current recommendations are that patients with severe disease (MDF ≥32) with or without encephalopathy and without contraindications for steroid use should be considered for a 4-week course of prednisone followed by a 2-week taper. Corticosteroids may increase the risk for infection in the treatment of alcoholic hepatitis. Pentoxifylline, which modifies TNFα, may also be considered, especially if steroids are contraindicated.

Liver transplantation may be an option. ALD is currently the second most common reason for liver transplantation in the United States. To be considered for transplantation, patients should have remained sober for >6 months and should have had addictive treatment. Recent studies have suggested that patients with severe alcoholic hepatitis should also be considered as eligible. The prognosis is excellent if relapse from drinking can be avoided. Relapse occurs in 15–30% of patients.

Other treatment methodologies in various stages of testing include other TNFα modifiers; antioxidant therapy with agents such as S-adenosyl-L-methionine (SAM-e), silymarin, or vitamin E; antifibrotics such as polyenylphosphatidylcholine (PPC); or other medications. Further studies are needed before these therapies can be recommended.

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Websites

Alcoholic Use Disorders Identification Test (AUDIT) website. https://www.drugabuse.gov/sites/default/files/files/AUDIT.pdf

OTHER LIVER DISEASES

Nonalcoholic Fatty Liver Disease

A relatively new condition described around 1980, nonalcoholic fatty liver disease (NAFLD) encompasses a wide clinical spectrum of patients whose liver histology is similar to those of patients with alcohol-induced hepatitis but without the requisite history. Women are affected more frequently than men. Many of these patients progress to cirrhosis. NAFLD is now the most common liver disease in the United States, occurring in ≤20% of the population in some studies. This

condition is common in obese patients, as well as in patients with type 2 diabetes mellitus. It may be a part of syndrome X, which includes obesity, diabetes mellitus, dyslipidemia, and hypertension. Clinical features include hepatomegaly (75%) and splenomegaly (25%), but there are no pathognomonic laboratory markers. Elevations of ALT and AST may be ≤5 times normal, with an AST/ALT ratio of <1. Evidence of steatosis can be seen on hepatic ultrasonography. Treatment includes weight reduction, treatment of diabetes, and treatment of lipid disorders. Specific pharmacologic therapy, such as incretin analogs, pentoxifylline, and other modalities, may be recommended in the future.

Wilson Disease

Wilson disease, which is characterized by hepatolenticular degeneration, is caused by abnormal metabolism of copper. It is inherited in an autosomal recessive pattern and has a prevalence in the general population of approximately 1 in 30,000. Although patients in asymptomatic stages may manifest only transaminasemia or Kayser-Fleischer rings (golden-greenish granular deposits in the limbus), hepatomegaly or splenomegaly may already be present. In most symptomatic patients (96%), the serum ceruloplasmin level is <20 mg/d. Patients >55 years of age who present with persistently elevated AST and ALT levels should probably be screened for Wilson disease with ceruloplasmin levels. In patients with more advanced disease, symptoms of acute hepatitis or cirrhosis may be present. Neurologic signs include dysarthria, tremors, abnormal movements, and psychological disturbances. HCC may occur in patients with advanced disease. Treatment includes penicillamine, trientine, or zinc salts.

Hemochromatosis

An inborn error of iron metabolism leading to increased iron absorption from the diet, hemochromatosis is associated with diabetes, bronze skin pigmentation, hepatomegaly, loss of libido, and arthropathy. Patients may also show signs of cardiac or endocrine disorders. Symptoms usually first manifest between 40 and 60 years of age, and men are 10 times more likely than women to be affected. Hemochromatosis is the most common inherited liver disease in people of European descent. Physical signs include hepatomegaly (95% of symptomatic patients), which precedes abnormal liver function tests. Cardiac involvement includes congestive heart failure and arrhythmias. Many patients have cirrhosis by the time they are symptomatic (50–70%), 20% have fibrosis, and 10–20% have neither. HCC is common in patients with cirrhosis (30%) and is now the most common cause of death. Laboratory findings include elevated serum iron concentration, serum ferritin, and transferrin saturation. Therapy involves treatment of the complications of hemochromatosis, removal of excess iron by phlebotomy, and, in patients with cirrhosis, surveillance for HCC and treatment of hepatic and cardiac failure.

Autoimmune Hepatitis

Autoimmune hepatitis is a hepatocellular inflammatory disease of unknown etiology. Diagnosis is based on histologic examination, hypergammaglobulinemia, and presence of serum autoantibodies. The condition may be difficult to discern from other causes of chronic liver disease, which need to be excluded before diagnosis. This condition may also occur with other autoimmune conditions such as Sjogren syndrome, psoriasis, ulcerative colitis, or hypothyroidism. Immunoserologic tests that are essential for diagnosis are assays for antinuclear antibodies (ANAs), smooth muscle antibodies (SMAs), antibodies to liver and kidney microsome type 1 (anti-LKM1), and anti-liver cytosol type 1 (anti-LC1), as well as perinuclear antineutrophil cytoplasmic antibodies (pANCAs). Treatment, when indicated, is usually immunosuppressive with either prednisone, azathioprine, or both.

Drug-Induced Liver Disease

More than 600 drugs or other medicinals have been implicated in liver disease. Worldwide, drug-induced liver disease represents approximately 3% of all adverse drug reactions; in the United States, >20% of cases of jaundice in the elderly are caused by drugs. Acetaminophen and other drugs account for 25–40% of fulminant hepatic failure. Diagnosis is based on the discovery of abnormalities in hepatic enzymes or the development of a hepatitis-like syndrome or jaundice. Most cases occur within 1 week to 3 months of exposure, and symptoms rapidly subside after cessation of the drug, returning to normal within 4 weeks of acute hepatocellular injury. Hepatic damage may manifest as acute hepatocellular injury (isoniazid, acetaminophen), cholestatic injury (contraceptive steroids, chlorpromazine), granulomatous hepatitis (allopurinol, phenylbutazone), chronic hepatitis (methotrexate), vascular injury (herbal tea preparations with toxic plant alkaloids), or neoplastic lesions (oral contraceptive steroids).

Statins, on the other hand, are widely used and can commonly cause mild liver enzyme elevations, but mild elevations of ALT or AST (<3 times the upper limit of normal) do not appear to contribute to liver toxicity.

A resource of use to determine the potential for hepatotoxicity of a supplement or drug is the following website: livertox.nih.gov.

Primary Biliary Cholangitis (Formerly Termed Primary Biliary Cirrhosis)

This autoimmune disease of uncertain etiology is manifested by inflammation and destruction of interlobular and septal bile ducts, which can cause chronic cholestasis and biliary cirrhosis. It is predominantly a disease of middle-aged women (female-to-male ratio of 9:1) and is particularly prevalent in northern Europe. The condition may be

diagnosed on routine testing or be suspected in women with symptoms of fatigue or pruritus, or in susceptible individuals with elevated serum alkaline phosphatase, cholesterol, and IgM levels. Antimitochondrial antibodies are frequently found. Ursodeoxycholic acid is the only therapy currently available, although some patients may benefit from liver transplantation.

Hepatic Tumors & Cysts

HCC is the most common malignant tumor of the liver; it is the fifth most common cancer in men and the eighth most common in women. Incidence increases with age, but the mean age in ethnic Chinese and African populations is lower. Signs of worsening cirrhosis may alert the clinician to consider HCC, but in many cases, the onset is subtle. There are no specific hepatic function tests to detect HCC, but elevated serum tumor markers, most notably α-fetoprotein, are useful. Ultrasonography can detect the majority of HCC but may not distinguish it from other solid lesions. CT and magnetic resonance imaging (MRI) are also helpful in making the diagnosis. Risk factors for HCC include HBV, HCV, all etiologic forms of cirrhosis, ingestion of foods with aflatoxin B_1, and smoking. In suspected HCC, diagnosis with CT scans or MRI is recommended. In moderate-risk patients, ultrasound studies every 6 months and possibly biopsies may be recommended if a definitive diagnosis cannot be made (see previous discussion in the sections on hepatitis).

Benign Tumors

Benign tumors include hepatocellular adenomas, which have become more common with the use of oral contraceptive steroids, and hepatic hemangiomas, which may occur with pregnancy or oral contraceptive steroid use and are the most common benign tumors of the liver.

Liver Abscesses

Liver abscesses can be the result of infections of the biliary tract or can have an extrahepatic source such as diverticulitis or inflammatory bowel disease. In ~40% of cases, no source of infection is found. The most common organisms are *Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, and *Streptococcus* species. Amebic liver abscesses are the most common extraintestinal manifestation of amebiasis, which occurs in >10% of the world's population and is most prevalent in the United States in young Hispanic adults. Amebic abscesses may have an acute presentation, with symptoms present for several weeks; few patients report typical intestinal symptoms such as diarrhea. Ultrasonography or CT scans with serologic tests such as enzyme-linked immunosorbent assay (ELISA) or indirect fluorescent antibody tests help confirm the diagnosis.

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PANCREATIC DISEASE

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ACUTE PANCREATITIS

ESSENTIALS OF DIAGNOSIS

► Sudden, severe, abdominal pain in epigastric area, with frequent radiation to the back.

► Elevated serum amylase and lipase.

► Elevated ALT (biliary pancreatitis).

► Evidence of etiology on ultrasound (biliary causes) or CT and MRI (other causes).

► General Considerations

Hospital admissions for acute pancreatitis are fairly frequent, and the most common causes vary with the age and sex of the patient. In the United States, gallstones and alcohol abuse are the most frequent etiologies (20–30%), but infectious causes such as mumps virus or parasitic disease should be considered, as well as medications, tumors, trauma, and metabolic conditions. Approximately 20% of cases are idiopathic. It is important to determine the etiology of pancreatitis because early recognition of acute biliary pancreatitis in particular may be important in selecting the appropriate therapeutic approach.

A more detailed discussion of gallstone pancreatitis appears earlier in this chapter.

► Clinical Findings

A. Symptoms and Signs

Abdominal pain—usually epigastric, which may radiate to the back—is an common presenting sign. However, the pain may not be significant, and some cases of acute pancreatitis are missed or diagnosed after more significant complications have occurred. Abdominal tenderness ranging from rigidity to mild tenderness may be present. Lack of a specific diagnostic test may affect the accuracy of an early diagnosis.

B. Laboratory Findings

Useful laboratory tests include serum amylase (elevated 3–5 times above normal), serum lipase (more than twice normal), and, for determining the etiology, liver function tests, especially ALT. Serum amylases that are significantly elevated in the presence of epigastric pain are strong indicators of pancreatitis. However, amylase clears rapidly from the blood, and levels may be normal even in patients with severe pancreatitis. A urine dipstick test for trypsinogen-2 may also be useful. The triglyceride levels should be checked, as well as calcium, in an attempt to identify pancreatitis associated with hyperlipemia and hyperparathyroidism.

C. Prognostic Tests and Patient Assessment

Over 20% of patients have a severe case of pancreatitis, and of these, a significant number die. It is therefore important to accurately assess and monitor the severity of the illness and treat accordingly. Attempts to quantify severity of disease have led to certain scoring criteria, but no specific scoring mechanism is reliable enough by itself to predict severity. A careful physician and laboratory assessment to ascertain fluid loss, hypovolemic shock, and organ dysfunction is crucial, and the American College of Gastroenterology states that the following patient-related risk factors for the development of severe disease need to be considered: patient age, comorbid health problems, body mass index, presence of systemic inflammatory response syndrome (SIRS), signs of hypovolemia such as elevated blood urea nitrogen and hematocrit, presence of pleural effusions and/or infiltrates, and altered mental status. Elevated pulse, respiratory rate, temperature, and white blood cell count are concerning for persistent SIRS.

D. Imaging Studies

Ultrasonography of the RUQ is helpful in identifying the etiology of pancreatitis and is usually the initial imaging study of choice. However, it has limited value in staging the severity of disease. (See the discussion earlier in the chapter on gallstone pancreatitis). Contrast-enhanced CT is the most common currently available imaging technique for staging the severity of pancreatitis and can determine the presence of glandular enlargement, intra- and extrapancreatic fluid collections, inflammation, necrosis, and abscesses. This study may not be necessary for patients with mild disease. MRCP may be just as accurate and has some advantages over contrast-enhanced CT in certain patients. MRI is an alternative when CT is not helpful or feasible.

▶ Complications

Complications include organ failure, cardiovascular collapse, and fluid collections around the pancreas. The latter may be asymptomatic or they may enlarge, causing pain, fever, and infection. Extrapancreatic infections, either bacteremia or pneumonia, have recently been shown to complicate the management of acute pancreatitis in a significant number of patients, usually within the first 2 weeks. Pancreatic pseudocysts may occur in patients with very high amylase levels and obstruction of the pancreatic duct. Pancreatic necrosis may also occur and can be fatal. Infection of necrotic tissue should be suspected in patients with unexpected deterioration, fever, and leukocytosis, and confirmed by CT scan and fine-needle aspiration. Sterile necrosis should probably be managed nonoperatively unless progressive deterioration occurs. Septic necrosis usually requires surgical débridement.

▶ Treatment

Patients who have the potential to develop severe pancreatitis, or who already have severe pain, dehydration, or vomiting, should be hospitalized and their hydration needs monitored closely. These patients should receive nothing by mouth and should be given intravenous pain medication. Patients should be monitored carefully to assess adequate renal function, because renal failure is a major cause of morbidity and mortality. Signs of worsening condition include rising hematocrit, tachycardia, and lack of symptom improvement in 48 hours.

Nutritional treatment has evolved in recent years, but areas of controversy remain. Increasing evidence indicates that in cases of mild pancreatitis, there is no benefit to nasogastric suction, and patients who are not vomiting may continue on oral fluids or resume oral fluids after the first week. There is also growing evidence that in severe pancreatitis, early enteral feeding within the first week may lower endotoxin absorption and reduce other complications. If patients cannot absorb adequate quantities via the enteric route, then parenteral feeding may be necessary. Total parenteral nutrition should otherwise be avoided in patients with mild and even severe pancreatitis.

The use of antibiotics is also controversial. Prophylactic antibiotics have been used in severe pancreatitis, but there is some concern that they may predispose patients to fungal infections. The general consensus is to use antibiotics, preferably broad-spectrum agents, for extrapancreatic infection or infected pancreatic necrosis, but not routinely.

Chronic Pancreatitis

Progression of inflammation and fibrotic changes can lead to a condition of chronic pancreatitis, impairing both exocrine and endocrine function. There is some debate regarding whether acute pancreatitis can eventually lead to chronic pancreatitis or whether chronic pancreatitis and recurrent acute pancreatitis are separate entities. Clinical conditions can vary, including abdominal pain, with occasional fat malabsorption and steatorrhea. Glucose intolerance and diabetes mellitus can also result. Alcohol, smoking, anatomic and obstructive abnormalities, and genetic factors may be

implicated as risk factors. Diagnosis is based on the clinical history, laboratory tests, and imaging, but sometimes the diagnosis is difficult, since there is an inconsistent picture regarding reliable clinical markers and sensitivity of imaging. However, CT imaging is the best initial imaging test. Treatment consists of pain management, lifestyle changes, enzymatic therapy if necessary, and invasive management if there are anatomic complications or obstructive stones.

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PANCREATIC CANCER

ESSENTIALS OF DIAGNOSIS

▶ Anorexia, jaundice, weight loss, epigastric pain radiating to back, dark urine, and light stools.

▶ Spiral CT of the abdomen or EUS showing evidence of tumor.

▶ CA 19-9 serum tumor marker.

▶ General Considerations

Although pancreatic cancer is diagnosed in only 30,000 patients each year in the United States, it is the fourth most common cause of death from cancer and the second most common gastrointestinal malignancy. Pancreatic cancer has a very poor prognosis: >80% of patients die within the first year, and the 5-year survival rate is <4%. In the vast majority of patients, the cancer is discovered at too late a stage to benefit from resection, and the response to chemotherapy is very poor. Over 90% of pancreatic cancers are ductal adenocarcinoma.

Cigarette smoking is the major risk factor established to date. Diet may also be a factor, with high intake of fat or meat and obesity associated with an increased risk; fruits, vegetables, and exercise help protect against pancreatic cancer. Likewise, a history of chronic pancreatitis is considered a risk factor, along with surgery for peptic ulcer disease, hereditary pancreatitis, and some genetic mutations (eg, *BRCA2*, associated with hereditary breast cancer). No guidelines currently exist regarding screening of the general population for pancreatic cancer, although some experts feel that patients with a family history of hereditary pancreatitis should be screened.

▶ Clinical Findings

A. Symptoms and Signs

The clinical presentation of pancreatic cancer can vary widely; tumors that occur in the head of the pancreas (two-thirds of all pancreatic cancer) may produce early signs of obstructive jaundice. Tumors in the body and tail of the pancreas may grow quite large and cause fewer signs of obstruction. Symptoms more likely to be associated with pancreatic cancer include abdominal pain, jaundice, dark urine, light-colored stools, and weight loss. Pain may be worse when the patient is lying flat or eating. Other physical signs associated with pancreatic cancer include Courvoisier sign (palpable, nontender gallbladder in a patient with jaundice).

B. Laboratory Findings

Laboratory evaluation should include liver function tests. The serum tumor antigen CA 19-9 may be useful in confirming a diagnosis but is not an appropriate screening tool. Other markers are under consideration.

C. Imaging Studies

There is some debate as to the best imaging study. RUQ transabdominal ultrasound is useful if patients present with abdominal pain and jaundice. If pancreatitis is included in the differential diagnosis, then contrast-enhanced CT scan may be more useful.

▶ Treatment

Because the only hope for a cure is surgical resection, staging of pancreatic tumors is important for management. The difficulty lies in identifying the small fraction of patients (<20%) who will benefit from surgery from those who will not—patients with metastatic disease who would otherwise be subjected to unnecessary invasive procedures and the resultant increased morbidity and mortality.

For patients with metastatic disease, chemotherapy and palliative care should be offered; surgery is avoided. Patients with advanced local disease but no metastases may benefit from radiotherapy and chemotherapy, and those without invasion or metastases may be candidates for resection. Even with resection, the outlook is poor (5-year survival rates of <25%). Radiation therapy may be useful in some patients with localized but nonresectable tumors, and chemotherapy (5-fluorouracil and gemcitabine) has some limited success.

Pain management can be a significant problem, and various modalities may need to be used. Biliary decompression may be required for jaundice.

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34

Abnormal Uterine Bleeding

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Patricia Evans, MD, MA

▶ General Considerations

Abnormal uterine bleeding (AUB), defined as premenopausal menstrual bleeding outside of the normal parameters of volume, duration, regularity, or frequency, affects 10–30% of women at some time during their lives. In 2011, the American College of Obstetricians and Gynecologists (ACOG) adopted a classification system known by the acronym PALM–COEIN, which classifies AUB by its causes: structural (**p**olyp, **a**denomyosis, **l**eiomyoma, **m**alignancy, and hyperplasia) and nonstructural (**c**oagulopathy, **o**vulatory dysfunction, **e**ndometrial, **i**atrogenic, and **n**ot yet classified). The recommendation of ACOG is to pair the term *abnormal uterine bleeding* with the letter denoting the cause in order to achieve uniformity in nomenclature and to eliminate the terminology of dysfunctional uterine bleeding. In addition, descriptive terms should be used instead of traditional Latin terms, such as *heavy menstrual bleeding* instead of *menorrhagia, intermenstrual bleeding* instead of *metrorrhagia,* and *infrequent* or *anovulatory bleeding* instead of *oligomenorrhea.*

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▶ Clinical Findings

A. Symptoms and Signs

1. History—The physician should try to establish whether the patient's pattern is cyclic or anovulatory. If the patient menstruates every 24–38 days, the cycle is consistent with an ovulatory pattern of bleeding. Patients often report breast discomfort or premenstrual symptoms with ovulatory bleeding. Although cycles may vary in length by several days, >10 days of variance raises the suspicion of anovulatory cycles. The patient should be asked to describe the current vaginal bleeding in terms of onset, frequency, duration, and severity. Although heavy menstrual bleeding is defined by >80 mL of blood loss, in practice, it is determined by patient report of excessive bleeding. Age, parity, sexual history, previous gynecologic disease, and obstetrical history will further assist the physician in focusing the evaluation of the woman with vaginal bleeding. The physician should ask about medications, including contraceptives, prescription medications, and over-the-counter (OTC) medications and supplements. The patient should be asked about any OTC preparations she might be taking. Patients may not be aware that herbal preparations may contribute to vaginal bleeding. Ginseng, which has estrogenic properties, can cause vaginal bleeding, and St. John's wort can interact with oral contraceptives to cause breakthrough bleeding. A review of symptoms should include questions regarding fever, fatigue, abdominal pain, hirsutism, galactorrhea, changes in bowel movements, and

heat/cold intolerance. A careful family history will aid in identifying patients with a predisposition to bleeding disorders, polycystic ovarian syndrome (PCOS), congenital adrenal hyperplasia, thyroid disease, fibroids, and cancer.

2. Physical examination—The physical examination for women complaining of AUB should begin with an evaluation of the patient's vital signs, body mass index, thyroid gland, and features of excess androgen (eg, hirsutism or acne). The pelvic examination will aid in identifying many causes of bleeding, including other sources of bleeding, anatomic abnormalities, infections, pregnancy, and signs of fibroids.

B. Evaluation

The evaluation of patients presenting with AUB includes a combination of laboratory testing, imaging studies, and sampling techniques. The evaluation is directed by both patient presentation and a risk evaluation for endometrial cancer.

C. Laboratory Findings

All patients presenting with AUB should be evaluated with a complete blood count, thyroid-stimulating hormone, urine or serum pregnancy test, and cervical cancer screening if due. If suggested by history or exam, testing for the sexually transmitted diseases gonorrhea, *Chlamydia,* and *Trichomonas* should be performed. Adolescents presenting with menorrhagia at menarche and patients with significant heavy bleeding or anemia should have an evaluation for coagulopathies, including platelet count, prothrombin time, and partial thromboplastin time. If no coagulation abnormality is found, then a test for von Willebrand disease (eg, von Willebrand factor antigen, ristocetin cofactor activity, or factor VIII) should be obtained. In patients with anovulatory bleeding and symptoms suggestive of PCOS or obesity, it is reasonable to check for testosterone and dehydroepiandrosterone sulfate. However, the diagnosis of PCOS may be made without laboratory testing if clinical hyperandrogenism is present with anovulatory cycles. In patients with significant hirsutism, a basal 17-hydroxyprogesterone (17-HP) should also be tested to screen for congenital adrenal hyperplasia.

D. Imaging Studies

1. Transvaginal ultrasound—Transvaginal ultrasonography can be used to evaluate the ovaries, uterus, and endometrial lining for abnormalities. An evaluation of the ovaries can assist in the diagnosis of PCOS because many patients with PCOS will have enlarged ovaries with multiple, small follicles. Transvaginal ultrasound is also useful for evaluating an enlarged uterus for the presence of fibroids. Fibroids will appear as hypoechoic, solid masses seen within the borders of the uterus. Serosal fibroids can be pedunculated and therefore can be seen outside the borders of the uterus.

In postmenopausal patients, an endovaginal ultrasound can be used to evaluate the thickness of the endometrial stripe. Postmenopausal patients with an endometrial stripe thicker than 4–5 mm should have a histologic biopsy. Evaluation of endometrial thickness in premenopausal patients has limited value due to the variations of endometrial thickness during the menstrual cycle. Premenopausal and perimenopausal patients with AUB at risk for endometrial cancer (eg, prolonged anovulation, over age 45) should have histologic sampling performed regardless of endometrial thickness. Hormone replacement therapy can also cause proliferation of a patient's endometrium, rendering an endovaginal evaluation less specific. The endovaginal ultrasound examination is less likely to detect intracavitary lesions, such as submucosal fibroids and polyps.

2. Sonohysterography—Saline infusion sonohysterography involves performing a transvaginal ultrasound following installation of saline into the uterus. This study is most useful in differentiating focal from diffuse endometrial abnormalities and for diagnosing intracavitary lesions. Detection of a focal abnormality indicates need for evaluation by hysteroscopy, and detection of an endometrial abnormality indicates the need to perform an endometrial biopsy or dilation and curettage (D&C). This can be considered as a study of first choice in premenopausal women with AUB given its higher sensitivity and specificity for uterine structural abnormalities than transvaginal ultrasound alone.

3. Magnetic resonance imaging—Magnetic resonance imaging (MRI) can be used to evaluate the uterine structure. The endometrium can be evaluated with an MRI, but the endometrial area seen on MRI does not correspond exactly to the endometrial stripe measured with ultrasound. In most situations, a transvaginal ultrasound is the preferred imaging modality, but if the patient cannot tolerate the procedure, MRI does provide an option for evaluation. MRI is better than ultrasound in distinguishing adenomyosis from fibroids, so if the history and examination suggest adenomyosis, an MRI may be the best first choice. MRI is also sometimes used to evaluate fibroids prior to uterine artery embolization or to map multiple myomas.

E. Special Examinations: Endometrial Sampling

The workup for endometrial cancer should be pursued most aggressively with patients at greatest risk for the disease, such as postmenopausal patients who present with vaginal bleeding and patients over 45 with any AUB. In these patients, the endometrium should be sampled using office-based endometrial biopsy or hysteroscopic dilatation and curettage if office sampling is inadequate or cannot be done. Alternatively, patients with postmenopausal bleeding can be evaluated with vaginal ultrasound initially, with endometrial biopsy if the endometrial stripe is >4 mm. In patients age <45 years, endometrial cancer is usually seen in obese

patients and/or patients who are chronically anovulatory. Therefore, patients under age 45 (particularly patients age 35–45) with risk factors for endometrial carcinoma (eg, obesity, PCOS, prolonged anovulatory cycles, or prolonged unopposed estrogen stimulation) or bleeding that does not respond to therapy should be evaluated for hyperplasia and neoplasm with an endometrial sample.

1. Endometrial biopsy—An endometrial biopsy is an adequate method of sampling the endometrial lining to identify histologic abnormalities. The rates of obtaining an adequate endometrial sample depend on the age of the patient. Many postmenopausal women will have an atrophic endometrium, so sampling in this group will more often result in an inadequate endometrial specimen for examination. In this situation, the clinician must use additional diagnostic studies to fully evaluate the cause of the vaginal bleeding.

2. Dilation and curettage—D&C provides a blind sampling of the endometrium. The D&C generally will provide sampling of less than half of the uterine cavity. The D&C is useful in patients with cervical stenosis or other anatomic factors that prevent an adequate endometrial biopsy.

3. Diagnostic hysteroscopy—Direct exploration of the uterus is useful in identifying structural abnormalities such as fibroids and endometrial polyps. In general, diagnostic hysteroscopy is combined with a D&C or endometrial biopsy to maximize identification of abnormalities.

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▶ Differential Diagnosis

The differential diagnosis of AUB, excluding pregnancy-related bleeding, encompasses a wide range of possible etiologies (Table 34–1).

Table 34–1. Differential diagnosis of abnormal uterine bleeding in the nonpregnant patient.

Diagnosis	Clinical Presentation
Structural 　Fibroids 　Adenomyosis 　Endometrial polyp 　Cervical polyp 　Endometriosis	Heavy, painful menstrual bleeding Intermenstrual spotting (polyps) Abnormal transvaginal ultrasound or sonohysterogram
Endometrial malignancy or hyperplasia	Anovulatory cycles Risk factors for endometrial cancer (age >35, obesity, PCOS, unopposed estrogen) Postmenopausal bleeding
Cervical cancer	Abnormal cervical pap smear Postcoital bleeding, irregular spotting
Bleeding disorder	Asymptomatic mucocutaneous bleeding, easy bruising Heavy menstrual bleeding since menarche
Physiologic anovulation	Adolescence Lactation Perimenopause
PCOS, adult-onset CAH	Hirsutism, acne, central obesity, and anovulatory cycles
Hyperthyroidism	Nervousness, heat intolerance, diarrhea, palpitations, weight loss
Hypothyroidism	Fatigue, cold intolerance, dry skin, hair loss, constipation, weight gain
Iatrogenic 　Hormonal contraceptives 　Hormone replacement 　Copper IUD 　Antipsychotics 　Anticoagulants	Bleeding correlating with medication use
Pelvic inflammatory disease Atypical presentation of *Chlamydia* cervicitis	High-risk sexual behavior, fever, pelvic pain, tenderness
Endometrial cause	Regular, heavy menses No structural cause found; may occur with menarche

CAH, congenital adrenal hyperplasia; IUD, intrauterine device; PCOS, polycystic ovarian syndrome.

A. Bleeding Secondary to Medications (Iatrogenic)

1. Hormonal contraception—Vaginal bleeding is a common side effect of all forms of contraception. Many patients starting oral contraceptive pills (OCPs) experience breakthrough

bleeding in the initial months. Lower estrogen OCPs have higher rates of spotting and breakthrough bleeding. Breakthrough bleeding is common among users of extended OCP regimens, and having the patient institute a 3-day hormone-free interval at the onset of breakthrough bleeding is an effective treatment for this side effect.

Irregular bleeding is also a common side effect of progestin-only contraceptive methods, such as progestin-only pills, depot medroxyprogesterone acetate (Depo-Provera), sub-dermal etonogestrel implants (Nexplanon), and levonorg-estrel intrauterine devices (IUDs). Although prevalence is difficult to estimate, most patients experience unscheduled bleeding with initiation, and although bleeding generally decreases with time, unscheduled bleeding is the most common reason for discontinuation of progestin-only methods.

2. Other medications—The copper IUD (Paragard) is known to cause heavier menstrual bleeding and dysmenor-rhea, although this can improve with time. It does not affect menstrual cycles. Anticoagulants and dopamine antagonists can also affect bleeding.

3. Hormone replacement therapy—Bleeding is common with hormone replacement therapy and can occur with both the continuous and sequential regimens. Approximately 40% of women starting continuous regimens will experience bleeding in the first 4–6 months after starting treatment.

B. Structural Causes

1. Endometrial and cervical polyps—Endometrial polyps can cause intermenstrual spotting, irregular bleeding, and/or heavy bleeding. Cervical polyps usually cause intermenstrual spotting or postcoital bleeding.

2. Adenomyosis—Adenomyosis is defined as the presence of endometrial glands within the myometrium. This is usu-ally asymptomatic, but patients can present with heavy or prolonged menstrual bleeding as well as dysmenorrhea. The dysmenorrhea can be severe and begin ≤1 week prior to menstruation. The appearance of symptoms usually occurs after age 40.

3. Fibroids—Fibroids, also called leiomyomas or myomas, are benign uterine tumors that are often asymptomatic. The most common symptoms associated with fibroid tumors are pelvic discomfort and AUB. Most commonly, patients with symptomatic fibroids experience either heavy or prolonged periods.

4. Malignancy and hyperplasia—Endometrial hyperplasia is an overgrowth of the glandular epithelium of the endome-trial lining. This usually occurs when a patient is exposed to unopposed estrogen, either iatrogenically, from obesity, or because of anovulation. The rate of neoplasms found with simple hyperplasia is 1%, and the rate with complex hyper-plasia reaches almost 30% when atypia is present. Patients having hyperplasia with atypia should have a hysterectomy because of the high incidence of subsequent endometrial cancer. Most patients without atypia will respond to proges-terone treatment. Endometrial ablation may also play a role in the treatment of hyperplasia.

Uterine cancer is the fourth most common cancer in women. Risk factors for endometrial cancer include nullipar-ity, late menopause (after age 52), obesity, diabetes, PCOS, unopposed estrogen therapy, tamoxifen, and a history of atypical endometrial hyperplasia. Endometrial cancer most often presents as postmenopausal bleeding, although overall, only 10% of patients with postmenopausal bleeding will have endometrial cancer. In the perimenopausal period, endome-trial cancer can present as irregular, typically heavy bleeding. The risk of endometrial cancer in premenopausal patients is low, but it can occur in patients who are obese with a long history of anovulatory cycles.

Vaginal bleeding is the most common symptom in patients with cervical cancer. The increased cervical friability associated with cervical cancer usually results in postcoital bleeding, but it also can appear as irregular or postmeno-pausal bleeding.

C. Nonstructural Causes

1. Coagulopathy—Formation of the platelet plug is the first step in hemostasis during menstruation. Patients with dis-orders that interfere with the formation of a normal platelet plug can experience heavy bleeding. The two most common disorders are von Willebrand disease and thrombocytope-nia. It has been estimated that 13–20% of patients with heavy menstrual bleeding have a coagulopathy, and this number is higher in adolescents.

2. Ovulatory

A. Anovulatory bleeding—There are multiple causes of anovulation, including physiologic and pathologic etiolo-gies. During the first year following menarche, anovulation is a normal result of an immature hypothalamic-pituitary-gonadal axis. Irregular ovulation is also a normal physiologic result of declining ovarian function during the perimeno-pausal years and the hormonal changes associated with lactation. Hyperandrogenic causes of anovulation include PCOS, adult-onset congenital adrenal hyperplasia, and androgen-producing tumors. Confirming the diagnosis of PCOS involves the evaluation of clinical features and endo-crine abnormalities and the exclusion of other etiologies. Patients with PCOS present with irregular, sometimes heavy bleeding due to prolonged estrogen stimulation and anovu-lation. In addition, patients can have hirsutism, acne, and central obesity. Endocrinologically, they can have increased testosterone activity, elevated luteinizing hormone concen-tration with a normal follicle-stimulating hormone level, and hyperinsulinemia due to insulin resistance. PCOS usually
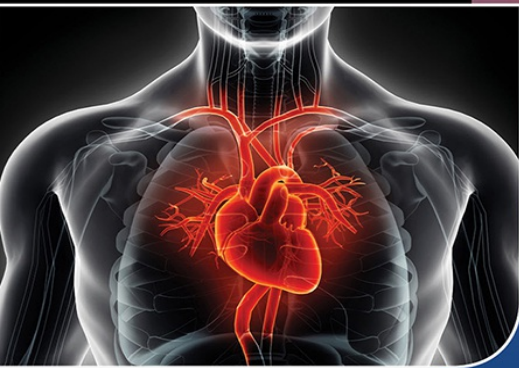
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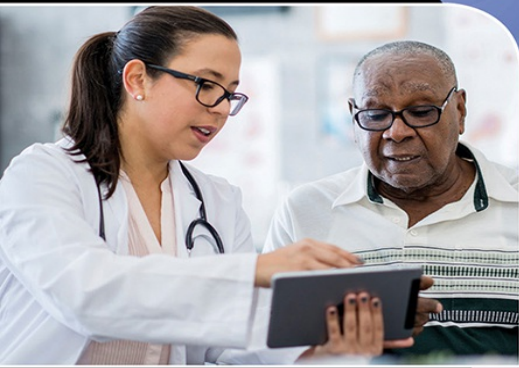
60th **ANNIVERSARY EDITION**

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Based on the National Health and Nutrition Survey through 2016, about 45% of adults in the United States have a blood pressure greater than 140/90 mm Hg or are being treated for hypertension. About 80% of people with hypertension are aware of the diagnosis and 75% are receiving treatment, but hypertension is controlled in only 52% of those affected. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise, but in individuals over age 50 years, the systolic pressure and pulse pressure are better predictors of complications than diastolic pressure. The prevalence of hypertension increases with age, and it is more common in blacks than in whites. Adequate blood pressure control reduces the incidence of acute coronary syndrome by 20–25%, stroke by 30–35%, and heart failure by 50%.

HOW IS BLOOD PRESSURE MEASURED & HYPERTENSION DIAGNOSED?

Blood pressure should be measured with a well-calibrated sphygmomanometer. The bladder width within the cuff should encircle at least 80% of the arm circumference. Readings should be taken after the patient has been resting comfortably, back supported in the sitting or supine position, for at least 5 minutes and at least 30 minutes after smoking or coffee ingestion. Automated office blood pressure readings, made with office-based devices that permit multiple automated measurements after a pre-programmed rest period, produce data that are independent of digit preference bias (tendency to favor numbers that end with zero or five) and the "white coat" phenomenon (where blood pressure is elevated in the clinic but normal at home). Blood pressure measurements taken outside the office environment, either by intermittent self-monitoring (home blood pressure) or with an automated device programmed to take measurements at regular intervals (ambulatory blood pressure) are more powerful predictors of outcomes and are advocated in clinical guidelines. Home measurements are also helpful in differentiating white coat hypertension from hypertension that is resistant to treatment, and in diagnosis of "masked hypertension" (where blood pressure is normal in the clinic but elevated at home). The cardiovascular risk associated with masked hypertension is similar to that observed in sustained hypertension.

A single elevated blood pressure reading is not sufficient to establish the diagnosis of hypertension. The major exceptions to this rule are hypertensive presentations with unequivocal evidence of life-threatening end-organ damage, as seen in hypertensive emergency, or in hypertensive urgency where blood pressure is greater than 220/125 mm Hg but life-threatening end-organ damage is absent. In less severe cases, the diagnosis of hypertension depends on a series of measurements of blood pressure, since readings can vary and tend to regress toward the mean with time. Patients whose initial blood pressure is in the hypertensive range exhibit the greatest fall toward the normal range between the first and second encounters. However, the concern for diagnostic precision needs to be balanced by an appreciation of the importance of establishing the diagnosis of hypertension as quickly as possible, since a 3-month delay in treatment of hypertension in high-risk patients is associated with a twofold increase in cardiovascular morbidity and mortality. Based on epidemiological data, the conventional 140/90 mm Hg threshold for the diagnosis of hypertension has been revised. The 2017 guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) suggest that, for conventional office-based measurement, **normal** be defined as less than 120/80 mm Hg, **elevated** as 120–129/less than 80 mm Hg, **stage 1** as 130–139/80–89 mm Hg and **stage 2** as greater than or equal to 140/90 mm Hg. As exemplified by Hypertension Canada's 2017 guidelines

([Figure 11–1](#)), automated and home blood pressure measurements have assumed greater prominence in the diagnostic algorithms published by many national hypertension workgroups. Equivalent blood pressure for these different modes of measurement are described in [Table 11–1](#).
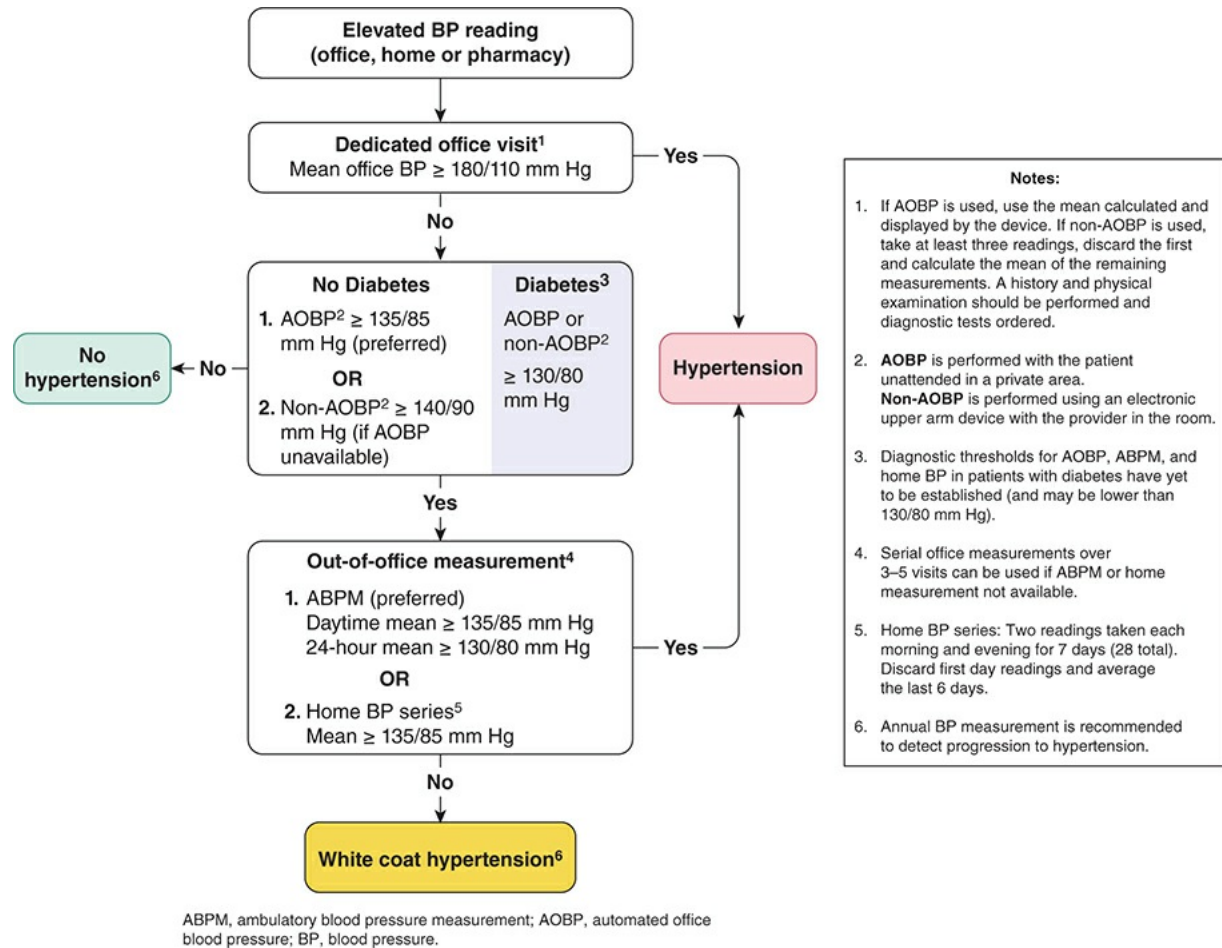

ABPM, ambulatory blood pressure measurement; AOBP, automated office blood pressure; BP, blood pressure.

Figure 11–1. According to these recommendations, if AOBP measurements are not available, blood pressures recorded manually in the office may be substituted if taken as the mean of the last two readings of three consecutive readings. Note that the blood pressure threshold for diagnosing hypertension is higher if recorded manually in these guidelines. If home blood pressure monitoring is unavailable, office measurements recorded over three to five separate visits can be substituted. (Reproduced, with permission, from Leung AA et al; Hypertension Canada. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017 May;33(5):557–76. Erratum in: Can J Cardiol. 2017 Dec;33(12):1733–4. Copyright © 2017 Canadian Cardiovascular Society. Published by Elsevier Inc. All rights reserved.)

Table 11–1. Corresponding blood pressure values across a range of blood pressure measurement methods.

Manual Measurement in Clinic[1]	Home Blood Pressure Measurement	Ambulatory Blood Pressure Measurement (Daytime)	Ambulatory Blood Pressure Measurement (Nighttime)	Ambulatory Blood Pressure Measurement (24-Hour)
120/80 mm Hg	120/80 mm Hg	120/80 mm Hg	100/65 mm Hg	115/75 mm Hg
130/80 mm Hg	130/80 mm Hg	130/80 mm Hg	110/65 mm Hg	125/75 mm Hg
140/90 mm Hg	135/85 mm Hg	135/85 mm Hg	120/70 mm Hg	130/80 mm Hg
160/100 mm Hg	145/90 mm Hg	145/90 mm Hg	140/85 mm Hg	145/90 mm Hg

[1]Clinic manual blood pressures are critically dependent on technique. The use of automated devices in an unattended setting typically result in systolic blood pressures 9–13 mm Hg lower than clinic manual pressures.
Data abstracted from Greenland P et al. The New 2017 ACC/AHA Guidelines "up the pressure" on diagnosis and treatment of hypertension. JAMA. 2017 Dec 5;318(21):2083–4.

Ambulatory blood pressure readings are normally lowest at night and the loss of this nocturnal dip is a dominant predictor of cardiovascular risk, particularly risk of thrombotic stroke. An accentuation of the normal morning increase in blood pressure is associated with increased likelihood of cerebral hemorrhage. Furthermore, variability of systolic blood pressure predicts cardiovascular events independently of mean systolic blood pressure.

It is important to recognize that the diagnosis of hypertension does not automatically entail drug treatment; this decision depends on the clinical setting, as discussed below.

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APPROACH TO HYPERTENSION

Etiology & Classification

A. Primary Essential Hypertension

"Essential hypertension" is the term applied to the 95% of hypertensive patients in which elevated blood pressure results from complex interactions between multiple genetic and environmental factors. The proportion regarded as "essential" will diminish with improved detection of clearly defined secondary causes and with better understanding of pathophysiology. Essential hypertension occurs in 10–15% of white adults and 20–30% of black adults in the United States. The onset is usually between ages 25 and 50 years; it is uncommon before age 20 years. The best understood pathways underlying hypertension include overactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems (RAAS), blunting of the pressure-natriuresis relationship, variation in cardiovascular and renal development, and elevated intracellular sodium and calcium levels.

Exacerbating factors include obesity, sleep apnea, increased salt intake, excessive alcohol use, cigarette smoking, polycythemia, nonsteroidal anti-inflammatory drug (NSAID) therapy, and low potassium intake. Obesity is associated with an increase in intravascular volume, elevated cardiac output, activation of the renin-angiotensin system, and, probably, increased sympathetic outflow. Lifestyle-driven weight reduction lowers blood pressure modestly, but the dramatic weight reduction following bariatric surgery results in improved blood pressure in most

patients, and actual remission of hypertension in 20–40% of cases. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) has been associated with improvements in blood pressure. Increased salt intake probably elevates blood pressure in some individuals so dietary salt restriction is recommended in patients with hypertension. Excessive use of alcohol also raises blood pressure, perhaps by increasing plasma catecholamines. Hypertension can be difficult to control in patients who consume more than 40 g of ethanol (two drinks) daily or drink in "binges." Cigarette smoking raises blood pressure by increasing plasma norepinephrine. Although the long-term effect of smoking on blood pressure is less clear, the synergistic effects of smoking and high blood pressure on cardiovascular risk are well documented. The relationship of exercise to hypertension is variable. Aerobic exercise lowers blood pressure in previously sedentary individuals, but increasingly strenuous exercise in already active subjects has less effect. The relationship between stress and hypertension is not established. Polycythemia, whether primary, drug-induced, or due to diminished plasma volume, increases blood viscosity and may raise blood pressure. NSAIDs produce increases in blood pressure averaging 5 mm Hg and are best avoided in patients with borderline or elevated blood pressures. Low potassium intake is associated with higher blood pressure in some patients; an intake of 90 mmol/day is recommended.

The complex of abnormalities termed the **"metabolic syndrome"** (upper body obesity, insulin resistance, and hypertriglyceridemia) is associated with both the development of hypertension and an increased risk of adverse cardiovascular outcomes. Affected patients usually also have low high-density lipoprotein (HDL) cholesterol levels and elevated catecholamines and inflammatory markers such as C-reactive protein.

B. Secondary Hypertension

Approximately 5% of patients have hypertension secondary to identifiable specific causes (Table 11–2). Secondary hypertension should be suspected in patients in whom hypertension develops at an early age or after the age of 50 years, and in those previously well controlled who become refractory to treatment. Hypertension resistant to maximum doses of three medications is another clue, although multiple medications are usually required to control hypertension in persons with diabetes. Secondary causes include genetic syndromes; kidney disease; renal vascular disease; primary hyperaldosteronism; Cushing syndrome; pheochromocytoma; coarctation of the aorta and hypertension associated with pregnancy, estrogen use, hypercalcemia, and medications.

Table 11–2. Identifiable causes of hypertension.

Sleep apnea
Drug-induced or drug-related
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Long-term corticosteroid therapy and Cushing syndrome
Pheochromocytoma
Coarctation of the aorta
Thyroid or parathyroid disease

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21;289(19):2560–72.

1. Genetic causes—Hypertension can be caused by mutations in single genes, inherited on a Mendelian basis. Although rare, these conditions provide important insight into blood pressure regulation and possibly the genetic basis of essential hypertension. Glucocorticoid remediable aldosteronism is an autosomal dominant cause of early-onset hypertension with normal or high aldosterone and low renin levels. In the syndrome of apparent mineralocorticoid excess, early-onset hypertension with hypokalemic metabolic alkalosis is inherited on an autosomal recessive basis. Although plasma renin is low and plasma aldosterone level is very low in these patients, aldosterone antagonists are effective in controlling hypertension. Glycyrrhetinic acid, found in licorice, causes increased blood pressure through inhibition of 11beta-hydroxysteroid dehydrogenase. The syndrome of hypertension exacerbated in pregnancy is inherited as an autosomal dominant trait. In these patients, a mutation in the mineralocorticoid receptor makes it abnormally responsive to progesterone and, paradoxically, to spironolactone. Gordon syndrome, or pseudohypoaldosteronism type II, presents with early-onset hypertension associated with

hyperkalemia, metabolic acidosis and relative suppression of aldosterone. Inheritance is most often autosomal dominant and the hypertension responds to a thiazide diuretic. The underlying mutations occur in one of several genes encoding proteins that regulate the thiazide-sensitive NaCl co-transporter in the distal nephron, leading to constitutive activation of sodium and chloride reabsorption.

2. Kidney disease—Renal parenchymal disease is the most common cause of secondary hypertension, which results from increased intravascular volume and increased activity of the RAAS. Increased sympathetic nerve activity may also contribute.

3. Renal vascular hypertension—Renal artery stenosis is present in 1–2% of hypertensive patients. The most common cause is atherosclerosis, but fibromuscular dysplasia should be suspected in women under 50 years of age. Excessive renin release occurs due to reduction in renal perfusion pressure, while attenuation of pressure natriuresis contributes to hypertension in patients with a single kidney or bilateral lesions. Activation of the renal sympathetic nerves may also be important.

Renal vascular hypertension should be suspected in the following circumstances: (1) the documented onset is before age 20 or after age 50 years, (2) the hypertension is resistant to three or more drugs, (3) there are epigastric or renal artery bruits, (4) there is atherosclerotic disease of the aorta or peripheral arteries (15–25% of patients with symptomatic lower limb atherosclerotic vascular disease have renal artery stenosis), (5) there is an abrupt increase (more than 25%) in the level of serum creatinine after administration of angiotensin-converting enzyme (ACE) inhibitors, or (6) episodes of pulmonary edema are associated with abrupt surges in blood pressure. (See Renal Artery Stenosis, Chapter 22.)

4. Primary hyperaldosteronism—Hyperaldosteronism should be considered in people with resistant hypertension, blood pressures consistently greater than 150/100 mm Hg, hypokalemia (although this is often absent), or adrenal incidentaloma, and in those with a family history of hyperaldosteronism. Mild hypernatremia and metabolic alkalosis may also occur. Hypersecretion of aldosterone is estimated to be present in 5–10% of hypertensive patients and, besides noncompliance, is the most common cause of resistant hypertension. The initial screening step is the simultaneous measurement of aldosterone and renin in blood in a morning sample collected after 30 minutes quietly seated. Hyperaldosteronism is suggested when the plasma aldosterone concentration is elevated (normal: 1–16 ng/dL) in association with suppression of plasma renin activity (normal: 1–2.5 ng/mL/h). However, the plasma aldosterone/renin ratio (normal less than 30) is not highly specific as a screening test. This is because renin levels may approach zero, which leads to exponential increases in the plasma aldosterone/renin ratio even when aldosterone levels are normal. Hence, an elevated plasma aldosterone/renin ratio should probably not be taken as evidence of hyperaldosteronism unless the aldosterone level is actually elevated.

During the workup for hyperaldosteronism, an initial plasma aldosterone/renin ratio can be measured while the patient continues taking usual medications. If under these circumstances the ratio proves normal or equivocal, medications that alter renin and aldosterone levels, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta-blockers, and clonidine, should be discontinued for 2 weeks before repeating the plasma aldosterone/renin ratio; spironolactone and eplerenone should be held for 4 weeks. Slow-release verapamil and alpha-receptor blockers can be used to control blood pressure during this drug washout period. Patients with a plasma aldosterone level greater than 16 ng/dL and an aldosterone/renin ratio of 30 or more might require further evaluation for primary hyperaldosteronism.

The lesion responsible for hyperaldosteronism is an adrenal adenoma or bilateral adrenal hyperplasia.

5. Cushing syndrome—Hypertension occurs in about 80% of patients with spontaneous Cushing syndrome. Excess glucocorticoid may act through salt and water retention (via mineralocorticoid effects), increased angiotensinogen levels, or permissive effects in the regulation of vascular tone.

Diagnosis and treatment of Cushing syndrome are discussed in Chapter 26.

6. Pheochromocytoma—Pheochromocytomas are uncommon; they are probably found in less than 0.1% of all patients with hypertension and in approximately two individuals per million population. However, autopsy studies indicate that pheochromocytomas are very often undiagnosed in life. The blood pressure elevation caused by the catecholamine excess results mainly from alpha-receptor–mediated vasoconstriction of arterioles, with a contribution from beta-1-receptor–mediated increases in cardiac output and renin release. Chronic vasoconstriction of the arterial and venous beds leads to a reduction in plasma volume and predisposes to postural hypotension. Glucose intolerance develops in some patients. Hypertensive crisis in pheochromocytoma may be precipitated by a

variety of drugs, including tricyclic antidepressants, antidopaminergic agents, metoclopramide, and naloxone. The diagnosis and treatment of pheochromocytoma are discussed in Chapter 26.

7. Coarctation of the aorta—This uncommon cause of hypertension is discussed in Chapter 10. Evidence of radial-femoral delay should be sought in all younger patients with hypertension.

8. Hypertension associated with pregnancy—Hypertension occurring de novo or worsening during pregnancy, including preeclampsia and eclampsia, is one of the most common causes of maternal and fetal morbidity and mortality (see Chapter 19). Autoantibodies with the potential to activate the angiotensin II type 1 receptor have been causally implicated in preeclampsia, in resistant hypertension, and in progressive systemic sclerosis.

9. Estrogen use—A small increase in blood pressure occurs in most women taking oral contraceptives. A more significant increase of 8/6 mm Hg systolic/diastolic is noted in about 5% of women, mostly in obese individuals older than age 35 who have been treated for more than 5 years. This is caused by increased hepatic synthesis of angiotensinogen. The lower dose of postmenopausal estrogen does not generally cause hypertension but rather maintains endothelium-mediated vasodilation.

10. Other causes of secondary hypertension—Hypertension has been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor denervation, compression of the rostral ventrolateral medulla, and increased intracranial pressure. A number of medications may cause or exacerbate hypertension—most importantly cyclosporine, tacrolimus, angiogenesis inhibitors, and erythrocyte-stimulating agents (such as erythropoietin). Decongestants, NSAIDs, cocaine, and alcohol should also be considered. Over-the-counter products should not be overlooked, eg, a dietary supplement marketed to enhance libido was found to contain yohimbine, an alpha-2–antagonist, which can produce severe rebound hypertension in patients taking clonidine.

When to Refer

Referral to a hypertension specialist should be considered in cases of severe, resistant or early-/late-onset hypertension or when secondary hypertension is suggested by screening.

Byrd JB et al. Primary aldosteronism. Circulation. 2018 Aug 21;138(8):823–35. [PMID: 30359120]

Owen JG et al. Bariatric surgery and hypertension. Am J Hypertens. 2017 Dec 8;31(1):11–7. [PMID: 28985287]

Raina R et al. Overview of monogenic or Mendelian forms of hypertension. Front Pediatr. 2019 Jul 1;7:263. [PMID: 31312622]

Raman G et al. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. Ann Intern Med. 2016 Nov 1;165(9):635–49. [PMID: 27536808]

Complications of Untreated Hypertension

Elevated blood pressure results in structural and functional changes in the vasculature and heart. Most of the adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. The excess morbidity and mortality related to hypertension approximately doubles for each 6 mm Hg increase in diastolic blood pressure. However, target-organ damage varies markedly between individuals with similar levels of office hypertension; home and ambulatory pressures are superior to office readings in the prediction of end-organ damage.

A. Hypertensive Cardiovascular Disease

Cardiac complications are the major causes of morbidity and mortality in primary (essential) hypertension. For any level of blood pressure, left ventricular hypertrophy is associated with incremental cardiovascular risk in association with heart failure (through systolic or diastolic dysfunction), ventricular arrhythmias, myocardial ischemia, and sudden death.

The occurrence of heart failure is reduced by 50% with antihypertensive therapy. Hypertensive left ventricular hypertrophy regresses with therapy and is most closely related to the degree of systolic blood pressure reduction. Diuretics have produced equal or greater reductions of left ventricular mass when compared with other drug classes. Conventional beta-blockers are less effective in reducing left ventricular hypertrophy but play a specific role in

patients with established coronary artery disease or impaired left ventricular function.

B. Hypertensive Cerebrovascular Disease and Dementia

Hypertension is the major predisposing cause of hemorrhagic and ischemic stroke. Cerebrovascular complications are more closely correlated with systolic than diastolic blood pressure. The incidence of these complications is markedly reduced by antihypertensive therapy. Preceding hypertension is associated with a higher incidence of subsequent dementia of both vascular and Alzheimer types. Home and ambulatory blood pressure may be a better predictor of cognitive decline than office readings in older people. Effective blood pressure control reduces the risk of cognitive dysfunction developing later in life.

C. Hypertensive Kidney Disease

Chronic hypertension is associated with injury to vascular, glomerular, and tubulointerstitial compartments within the kidney, accounting for about 25% of end-stage kidney disease. Nephrosclerosis is particularly prevalent in blacks, in whom susceptibility is linked to *APOL1* mutations and hypertension results from kidney disease rather than causing it.

D. Aortic Dissection

Hypertension is a contributing factor in many patients with dissection of the aorta. Its diagnosis and treatment are discussed in Chapter 12.

E. Atherosclerotic Complications

Most Americans with hypertension die of complications of atherosclerosis, but antihypertensive therapy seems to have a lesser impact on atherosclerotic complications compared with the other effects of treatment outlined above. Prevention of cardiovascular outcomes related to atherosclerosis probably requires control of multiple risk factors, of which hypertension is only one.

Seccia TM et al. Hypertensive nephropathy. Moving from classic to emerging pathogenetic mechanisms. J Hypertens. 2017 Feb;35(2):205–12. [PMID: 27782909]

Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019 Sep 17;140(12):976–8. [PMID: 31525101]

Clinical Findings

The clinical and laboratory findings are mainly referable to involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

A. Symptoms

Mild to moderate primary (essential) hypertension is largely asymptomatic for many years. The most frequent symptom, headache, is also nonspecific. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy).

Hypertension in patients with pheochromocytomas that secrete predominantly norepinephrine is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia; malignant hypertension is rare. Chronic hypertension often leads to left ventricular hypertrophy and diastolic dysfunction, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries. Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema, which is reversible.

B. Signs

Like symptoms, physical findings depend on the cause of hypertension, its duration and severity, and the degree of

effect on target organs.

1. Blood pressure—Blood pressure is taken in both arms and, if lower extremity pulses are diminished or delayed, in the legs to exclude coarctation of the aorta. If blood pressure differs between right and left arms, the higher reading should be recorded as the actual blood pressure and subclavian stenosis suspected in the other arm. An orthostatic drop of at least 20/10 mm Hg is often present in pheochromocytoma. Older patients may have falsely elevated readings by sphygmomanometry because of noncompressible vessels. This may be suspected in the presence of Osler sign—a palpable brachial or radial artery when the cuff is inflated above systolic pressure. Occasionally, it may be necessary to make direct measurements of intra-arterial pressure, especially in patients with apparent severe hypertension who do not tolerate therapy.

2. Retinas—Narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, or hypertensive retinopathy are associated with a worse prognosis. the typical changes of severe hypertensive retinopathy are shown in Figure 11–2.

Figure 11–2. Severe, chronic hypertensive retinopathy with hard exudates, increased vessel light reflexes, and sausage-shaped veins. (Used, with permission, from Richard E. Wyszynski, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill, 2016.)

3. Heart—A left ventricular heave indicates severe hypertrophy. Aortic regurgitation may be auscultated in up to 5% of patients, and hemodynamically insignificant aortic regurgitation can be detected by Doppler echocardiography in 10–20%. A presystolic (S_4) gallop due to decreased compliance of the left ventricle is quite common in patients in sinus rhythm.

4. Pulses—Radial-femoral delay suggests coarctation of the aorta; loss of peripheral pulses occurs due to atherosclerosis, less commonly aortic dissection, and rarely Takayasu arteritis, all of which can involve the renal arteries.

C. Laboratory Findings

Recommended testing includes the following: hemoglobin; serum electrolytes and serum creatinine; fasting blood sugar level (hypertension is a risk factor for the development of diabetes, and hyperglycemia can be a presenting feature of pheochromocytoma); plasma lipids (necessary to calculate cardiovascular risk and as a modifiable risk factor); serum uric acid (hyperuricemia is a relative contraindication to diuretic therapy); and urinalysis.

D. Electrocardiography and Chest Radiographs

Electrocardiographic criteria are highly specific but not very sensitive for left ventricular hypertrophy. The "strain" pattern of ST–T wave changes is a sign of more advanced disease and is associated with a poor prognosis. A chest radiograph is not necessary in the workup for uncomplicated hypertension.

E. Echocardiography

The primary role of echocardiography should be to evaluate patients with clinical symptoms or signs of cardiac

disease.

F. Diagnostic Studies

Additional diagnostic studies are indicated only if the clinical presentation or routine tests suggest secondary or complicated hypertension. These may include 24-hour urine free cortisol, urine or plasma metanephrines, and plasma aldosterone and renin concentrations to screen for endocrine causes of hypertension. Renal ultrasound will detect structural changes (such as polycystic kidneys, asymmetry, and hydronephrosis); echogenicity and reduced cortical volume are reliable indicators of advanced chronic kidney disease. Evaluation for renal artery stenosis should be undertaken in concert with subspecialist consultation.

G. Summary

Since most hypertension is essential or primary, few studies are necessary beyond those listed above. If conventional therapy is unsuccessful or if secondary hypertension is suspected, further studies and perhaps referral to a hypertension specialist are indicated.

Katsi V et al. Impact of arterial hypertension on the eye. Curr Hypertens Rep. 2012 Dec;14(6):581–90. [PMID: 22673879]

Nonpharmacologic Therapy

Lifestyle modification may have an impact on morbidity and mortality and is recommended in all patients with elevated blood pressure. A diet rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fats (DASH diet) has been shown to lower blood pressure. Increased dietary fiber lowers blood pressure. For every 7 g of dietary fiber ingested, cardiovascular risk could be lowered by 9%. The effect of diet on blood pressure may be mediated by shifts in the microbial species in the gut, the intestinal microbiota. Hand squeezing exercises three times a week can lower systolic blood pressure by 6 mm Hg. The protocol comprises four repeats of 2 minutes at 30% of maximum force (using a handheld dynamometer) with 1- to 3-minute rest intervals between squeezes. Additional lifestyle changes, listed in Table 11–3, can prevent or mitigate hypertension or its cardiovascular consequences.

Table 11–3. Lifestyle modifications to manage hypertension.[1]

Modification	Recommendation	Approximate Systolic BP Reduction, Range
Weight reduction	Maintain normal body weight (BMI, 18.5–24.9)	5–20 mm Hg/10 kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated fat and total fat	8–14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/day (2.4 g sodium or 6 g sodium chloride)	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than two drinks per day (1 oz or 30 mL ethanol [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than one drink per day in women and lighter-weight persons	2–4 mm Hg

[1]For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose- and time-dependent and could be higher for some individuals.
BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension.
Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21;289(19):2560–72.

Appel LJ. The effects of dietary factors on blood pressure. Cardiol Clin. 2017 May;35(2):197–212. [PMID: 28411894]

Marques FZ et al. Beyond gut feelings: how the gut microbiota regulates blood pressure. Nat Rev Cardiol. 2018 Jan;15(1):20–32. [PMID: 28836619]

Smart NA et al. An evidence-based analysis of managing hypertension with isometric resistance exercise—are the guidelines current? Hypertens Res. 2020 Apr;43(4):249–54. [PMID: 31758166]

Who Should Be Treated With Medications?

Treatment should be offered to all persons in whom blood pressure reduction, irrespective of initial blood pressure levels, will reduce cardiovascular risk with an acceptably low rate of medication-associated adverse effects. The American College of Cardiology and the American Heart Association (ACC/AHA), Hypertension Canada (HC), and the European Society of Hypertension and European Society of Cardiology (ESH/ESC) have developed independent guidelines for the evaluation and management of hypertension. There is broad agreement that drug treatment is necessary in those with office-based blood pressures exceeding 160/100 mm Hg, irrespective of cardiac risk. Similarly, the American, Canadian, and European guidelines agree that treatment thresholds should be lower in the presence of elevated cardiovascular risk. American guidelines stand apart in recommending initiation of antihypertensive pharmacotherapy in those with stage 1 hypertension (140–159/90–99 mm Hg) even if cardiovascular risk is not elevated. By contrast, the Canadian guidelines suggest lifestyle modifications in this low-cardiovascular-risk group, while the European guidelines recommend initiation of pharmacotherapy only if elevated pressure in this low-risk population persists after lifestyle modification. There is no outcomes evidence that mortality or risk of cardiovascular events can be reduced by treating mild hypertension (140/90–160/100 mm Hg) in low-risk individuals. Table 11–4 compares these three sets of guidelines. Since evaluation of total cardiovascular risk (Table 11–5) is important in deciding who to treat with antihypertensive medications, risk calculators are essential clinical tools. The ACC has an online toolkit relevant to primary prevention (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/), and an associated app called ASCVD Risk Estimator Plus (downloadable at https://www.acc.org/ASCVDApp).

Table 11–4. Comparison of blood pressure treatment thresholds from the 2017 ACC/AHA guidelines, the 2018 Hypertension Canada guidelines, and the 2018 ESH/ESC guidelines.

Cardiovascular Risk	Guidelines[1]	Threshold for Pharmacotherapy (mm Hg)	Target (mm Hg)
Nonelevated	ACC/AHA	> 140/90	< 130/80 (reasonable)
	Hypertension Canada	> 160/100	< 140/90 (< 130/80 for diabetes)
	ESH/ESC	> 140/90[2]	All < 140/90, most < 130/80, not < 120
Elevated	ACC/AHA	< 130/80	< 130/80 (recommended)
	Hypertension Canada	> 140 systolic[3]	< 120 systolic
	ESH/ESC	> 130/80[3]	120–130/< 80
Elderly	ACC/AHA > 65 yr	> 130/80	< 130 systolic
	Hypertension Canada[4]	Not specified[4]	Not specified[4]
	ESH/ESC > 65 yr	> 140/90[5]	130–140/> 80[6]

[1]In all three sets of guidelines, blood pressure values are based upon nonautomated office blood pressure readings.
[2]Consider drug treatment if lifestyle changes fail to control blood pressure.
[3]Consider drug treatment if very high risk, eg, established cardiovascular disease, especially coronary disease. **Note:** The > 130/80 mm Hg threshold for treatment of high-risk patients in the Canadian guidelines refers to automated blood pressure readings, which are lower than nonautomated readings.
[4]Recommendations for persons > 75 years are not explicitly stated in the Hypertension Canada guidelines. They removed separate goals for the elderly, but consider age > 75 years to be a risk signifier triggering an approach that many would view as overly aggressive in the extremely old.
[5]The European guidelines indicate a slightly more conservative treatment threshold of > 160/90 mm Hg for those > 80 years.
[6]This target range is also suggested in the European guidelines for patients > 80 years.
ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

Table 11–5. Cardiovascular risk factors.

Major risk factors
Hypertension[1]
Cigarette smoking
Obesity (BMI ≥ 30)[1]
Physical inactivity
Dyslipidemia[1]
Diabetes mellitus[1]
Microalbuminuria or estimated GFR < 60 mL/min
Age (> 55 years for men, > 65 years for women)
Family history of premature cardiovascular disease (< 55 years for men, < 65 years for women)
Target-organ damage
Heart
Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

[1]Components of the metabolic syndrome.

BMI, body mass index; GFR, glomerular filtration rate.

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21; 289(19):2560–72.

Goals of Treatment

Traditionally, the most widely accepted goal for blood pressure management has been less than 140/90 mm Hg. However, observational studies suggest that there does not seem to be a blood pressure level below which decrements in cardiovascular risk taper off, and a number of randomized controlled trials have suggested that treatment to blood pressure targets considerably below 140 mm Hg may benefit certain patient groups.

The SPRINT study suggests that outcomes improve in nondiabetic patients with considerably elevated cardiovascular risk when treatment lowers systolic pressure to less than 120 mm Hg compared to less than 140 mm Hg. On the other hand, in the HOPE3 study of largely nondiabetic patients at somewhat lower risk than those in SPRINT, reducing blood pressure by an average of 6/3 mm Hg systolic/diastolic from a baseline of 138/82 mm Hg provided no significant outcomes benefits. Therefore, it appears that blood pressure targets should be lower in people at greater estimated cardiovascular risk. In response to the SPRINT study, the 2018 Hypertension Canada guidelines urge prescribers to consider a blood pressure goal of less than 120/80 mm Hg in patients considered at elevated risk for cardiovascular events. The 2017 ACC/AHA guidelines take a different approach by defining a 130/80 mm Hg goal as "reasonable" in nonelevated risk patients, strengthening this to "recommended" in elevated risk hypertensive patients. The 2018 ESH/ESC guidelines specify a target of less than 140 mm Hg systolic for all, and less than 130 mm Hg for most if tolerated. There is a trend toward recommending similar treatment targets in the elderly; this topic is discussed in greater detail below. Some experts note that manual office measurements of around 130/80 mm Hg are likely to approximate the lower blood pressure targets specified in the SPRINT study, which used automated office blood pressure measuring devices that have been demonstrated to read as much as 16/7 mm Hg lower than manual office readings. The 2018 Canadian guidelines acknowledge this disparity in measurement methods by specifying that automated office devices should be used in the monitoring of patients selected for the aggressive blood pressure goal of less than 120/80 mm Hg. Table 11–4 compares the treatment

threshold and target recommendations laid out in the American, Canadian, and European guidelines.

Treatment to blood pressures less than 130 mm Hg systolic seems especially important in stroke prevention. The ACCORD study examined the effect of treatment of systolic pressures to below 130–135 mm Hg in patients with diabetes. Although the lower treatment goal significantly increased the risk of serious adverse effects (with no additional gain in terms of heart, kidney, or retinal disease), there was a significant additional reduction in the risk of stroke. Lower targets might be justified in diabetic patients at high risk for cerebrovascular events.

Similarly, in the SPS3 trial in patients who have had a lacunar stroke, treating the systolic blood pressure to less than 130 mm Hg (mean systolic blood pressure of 127 mm Hg among treated versus mean systolic blood pressure 138 mm Hg among untreated patients) probably reduced the risk of recurrent stroke (and with an acceptably low rate of adverse effects from treatment). Blood pressure management in acute stroke is discussed below.

How Low To Go?

Although observational studies indicate that the blood pressure-risk relationship holds up at levels considerably below 120 mm Hg, there is uncertainty about whether this is true for treated blood pressure. This question was addressed in a secondary analysis of data from the ONTARGET and TRANSCEND studies in which participants with elevated cardiovascular risk but no history of stroke were treated with telmisartan (plus or minus ramipril), or placebo. The risk of the composite cardiovascular endpoint was lowest at a treated systolic blood pressure range between 120 mm Hg and 140 mm Hg. Increased risk was observed at blood pressures below and above this range. The risk of stroke was the only exception, with incremental benefit observed below a treated systolic of 120 mm Hg. With respect to diastolic blood pressure on treatment, composite risk began to increase at levels below 70 mm Hg. This suggests that the blood pressure–cardiovascular risk relationship evident in observational studies may not hold in the case of treated blood pressure and that there are grounds for a degree of caution in treating below a systolic pressure of 120 mm Hg.

In seeking to simplify decision making in the treatment of hypertension, some authors have suggested that a systolic blood pressure goal in the 120–130 mm Hg range would be safe and effective in high-risk patients, and a systolic blood pressure of around 130 mm Hg would be reasonable in lower-risk patients.

Data from multiple studies indicate that statins should be part of the strategy to reduce overall cardiovascular risk. The HOPE3 study of persons at intermediate cardiovascular risk showed that 10 mg of rosuvastatin reduced average low-density lipoprotein (LDL) cholesterol from 130 mg/dL to 90 mg/dL (3.36–2.33 mmol/L), and significantly reduced the risk of multiple cardiovascular events, including myocardial infarction and coronary revascularization. Low-dose aspirin (81 mg/day) is likely to be beneficial in patients older than age 50 with either target-organ damage or elevated total cardiovascular risk (greater than 20–30%). Care should be taken to ensure that blood pressure is controlled to the recommended levels before starting aspirin to minimize the risk of intracranial hemorrhage. Data do not support the routine use of aspirin for prophylaxis in low-risk patients, including those over 65 years of age.

ACCORD Study Group; Cushman WC et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575–85. [PMID: 20228401]

Böhm M et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet. 2017 Jun 3;389(10085):2226–37. [PMID: 28390695]

Lonn EM et al; HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016 May 26;374(21):2009–20. [PMID: 27041480]

Ridker PM. Should aspirin be used for primary prevention in the post-statin era? N Engl J Med. 2018 Oct 18;379(16):1572–4. [PMID: 30332575]

Ruiz-Hurtado G et al. Has the SPRINT trial introduced a new blood-pressure goal in hypertension? Nat Rev Cardiol. 2017 Sep;14(9):560–6. [PMID: 28492286]

Sheppard JP et al. Benefits and harms of antihypertensive treatment in low-risk patients with mild hypertension. JAMA Intern Med. 2018 Dec; 178(12):1626–34. [PMID: 30383082]

SPRINT Research Group; Wright JT Jr et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015 Nov 26;373(22):2103–16. [PMID: 26551272]

Williams B et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). Blood Press. 2018 Dec;27(6):314–40. [PMID: 30380928]

Yusuf S et al; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular

DRUG THERAPY: CURRENT ANTIHYPERTENSIVE AGENTS

There are many classes of antihypertensive drugs of which six (ACE inhibitors, ARBs, renin inhibitors, calcium channel blockers, diuretics, and beta-blockers) are suitable for initial therapy based on efficacy and tolerability. A number of considerations enter into the selection of the initial regimen for a given patient. These include the weight of evidence for beneficial effects on clinical outcomes, the safety and tolerability of the drug, its cost, demographic differences in response, concomitant medical conditions, and lifestyle issues. The specific classes of antihypertensive medications are discussed below, and guidelines for the choice of initial medications are offered.

A. Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are commonly used as the initial medication in mild to moderate hypertension (Table 11–6). Their primary mode of action is inhibition of the RAAS, but they also inhibit bradykinin degradation, stimulate the synthesis of vasodilating prostaglandins, and can reduce sympathetic nervous system activity. These latter actions may explain why they exhibit some effect even in patients with low plasma renin activity. ACE inhibitors appear to be more effective in younger white patients. They are relatively less effective in blacks and older persons and in predominantly systolic hypertension. Although as single therapy they achieve adequate antihypertensive control in only about 40–50% of patients, the combination of an ACE inhibitor and a diuretic or calcium channel blocker is potent.

Table 11–6. Antihypertensive drugs: renin and ACE inhibitors and angiotensin II receptor blockers.

Drug	Proprietary Name	Initial Oral Dosage	Dosage Range	Cost per Unit	Cost of 30 Days of Treatment (Average Dosage)[1]	Adverse Effects	Comments
Renin Inhibitors							
Aliskiren	Tekturna	150 mg once daily	150–300 mg once daily	$7.48/150 mg	$224.41	Angioedema, hypotension, hyperkalemia. Contraindicated in pregnancy.	Probably metabolized by CYP3A4. Absorption is inhibited by high-fat meal.
Aliskiren and HCTZ	Tekturna HCT	150 mg/12.5 mg once daily	150 mg/12.5 mg–300 mg/ 25 mg once daily	$8.31/150 mg/ 12.5 mg	$249.36		
ACE Inhibitors							
Benazepril	Lotensin	10 mg once daily	5–40 mg in 1 or 2 doses	$0.95/20 mg	$28.50	Cough, hypotension, dizziness, kidney dysfunction, hyperkalemia, angioedema; taste alteration and rash (may be more frequent with captopril); rarely, proteinuria, blood dyscrasia. Contraindicated in pregnancy.	More fosinopril is excreted by the liver in patients with kidney dysfunction (dose reduction may or may not be necessary). Captopril and lisinopril are active without metabolism. Captopril, enalapril, lisinopril, and quinapril are approved for heart failure.
Benazepril and HCTZ	Lotensin HCT	5 mg/6.25 mg once daily	5 mg/6.25 mg–20 mg/ 25 mg	$1.07/any dose	$32.21		
Benazepril and amlodipine	Lotrel	10 mg/2.5 mg once daily	10 mg/2.5 mg–40 mg/ 10 mg	$3.32/20 mg/ 10 mg	$99.60		
Captopril	Capoten	25 mg twice daily	50–450 mg in 2 or 3 doses	$0.65/25 mg	$19.50		
Captopril and HCTZ	Capozide	25 mg/15 mg twice daily	25 mg/15 mg–50 mg/ 25 mg	$2.85/25 mg/ 15 mg	$171.00		
Enalapril	Vasotec	5 mg once daily	5–40 mg in 1 or 2 doses	$0.95/20 mg	$28.50		
Enalapril and HCTZ	Vaseretic	5 mg/12.5 mg once daily	5 mg/12.5 mg–10 mg/ 25 mg	$1.22/10 mg/ 25 mg	$36.60		
Fosinopril	Monopril	10 mg once daily	10–80 mg in 1 or 2 doses	$0.29/20 mg	$8.70		
Fosinopril and HCTZ	Monopril-HCT	10 mg/12.5 mg once daily	10 mg/12.5 mg–20 mg/ 12.5 mg	$1.48/any dose	$44.40		
Lisinopril	Prinivil, Zestril	5–10 mg once daily	5–40 mg once daily	$0.08/20 mg	$2.45		
Lisinopril and HCTZ	Prinzide or Zestoretic	10 mg/12.5 mg once daily	10 mg/12.5 mg–20 mg/ 12.5 mg	$0.14/20 mg/ 12.5 mg	$4.20		
Moexipril	Univasc	7.5 mg once daily	7.5–30 mg in 1 or 2 doses	$1.39/7.5 mg	$41.70		
Moexipril and HCTZ	Uniretic	7.5 mg/12.5 mg once daily	7.5 mg/12.5 mg–15 mg/ 25 mg	$1.70/15 mg/ 12.5 mg	$51.00		

Perindopril	Aceon	4 mg once daily	4–16 mg in 1 or 2 doses	$2.80/8 mg	$84.00		
Perindopril and amlodipine	Prestalia	3.5 mg/2.5 mg once daily	3.5 mg/2.5–14 mg/10 mg once daily	$6.81/7 mg/ 5 mg	$204.30		
Quinapril	Accupril	10 mg once daily	10–80 mg in 1 or 2 doses	$1.22/20 mg	$36.60		
Quinapril and HCTZ	Accuretic	10 mg/12.5 mg once daily	10 mg/12.5 mg–20 mg/ 25 mg	$1.22/20 mg/ 12.5 mg	$36.60		
Ramipril	Altace	2.5 mg once daily	2.5–20 mg in 1 or 2 doses	$1.80/5 mg	$54.00		
Trandolapril	Mavik	1 mg once daily	1–8 mg once daily	$1.21/4 mg	$36.30		
Trandolapril and verapamil	Tarka	2 mg/180 mg ER once daily	2 mg/180 mg ER–8 mg/ 480 mg ER	$5.29/any dose	$158.70		
Angiotensin II Receptor Blockers							
Azilsartan	Edarbi	40 mg once daily	40–80 mg once daily	$8.54/80 mg	$256.20	Hyperkalemia, kidney dysfunction, rare angioedema. Combinations have additional side effects. Contraindicated in pregnancy.	Losartan has a flat dose-response curve. Valsartan and irbesartan have wider dose-response ranges and longer durations of action. Addition of low-dose diuretic (separately or as combination pills) increases the response.
Azilsartan and chlorthalidone	Edarbychlor	40 mg/12.5 mg once daily	40 mg/12.5–40 mg/25 mg once daily	$8.06/any dose	$241.80		
Candesartan cilexitil	Atacand	16 mg once daily	8–32 mg once daily	$3.06/16 mg	$91.80		
Candesartan cilexitil and HCTZ	Atacand HCT	16 mg/12.5 mg once daily	32 mg/12.5 mg once daily	$4.72/16 mg/ 12.5 mg	$141.60		
Eprosartan	Teveten	600 mg once daily	400–800 mg in 1–2 doses	$3.43/600 mg	$102.90		
Irbesartan	Avapro	150 mg once daily	150–300 mg once daily	$0.46/150 mg	$13.80		
Irbesartan and HCTZ	Avalide	150 mg/12.5 mg once daily	150–300 mg irbesartan once daily	$0.67/150 mg/ 12.5 mg	$20.10		
Losartan and HCTZ	Hyzaar	50 mg/12.5 mg once daily	50 mg/12.5 mg–100 mg/ 25 mg tablets once daily	$2.47/50 mg/ 12.5 mg/tablet	$74.10		
Olmesartan	Benicar	20 mg once daily	20–40 mg once daily	$6.28/20 mg	$188.40		
Olmesartan and HCTZ	Benicar HCT	20 mg/12.5 mg once daily	20 mg/12.5 mg–40 mg/ 25 mg once daily	$6.28/20 mg/ 12.5 mg	$188.40		
Olmesartan and amlodipine	Azor	20 mg/5 mg once daily	20 mg/5 mg–40 mg/10 mg	$3.03/20 mg/ 5 mg	$90.90		
Olmesartan and amlodipine and HCTZ	Tribenzor	20 mg/5 mg/12.5 mg once daily	20 mg/5 mg/12.5 mg – 40 mg/ 10 mg/25 mg once daily	$4.54/20 mg/ 5 mg/12.5 mg	$136.20		
Telmisartan	Micardis	40 mg once daily	20–80 mg once daily	$4.34/40 mg	$130.20		
Telmisartan and HCTZ	Micardis HCT	40 mg/12.5 mg once daily	40 mg/12.5 mg–80 mg/ 25 mg once daily	$4.83/40 mg/12.5 mg	$144.90		
Telmisartan and amlodipine	Twynsta	40 mg/5 mg once daily	40 mg/5 mg–80 mg/10 mg once daily	$5.20/any dose	$156.00		
Valsartan	Diovan	80 mg once daily	80–320 mg once daily	$2.09/160 mg	$62.70		
Valsartan and HCTZ	Diovan HCT	80 mg/12.5 mg once daily	80–320 mg valsartan once daily	$4.84/160 mg/ 12.5 mg	$145.20		
Valsartan and amlodipine	Exforge	160 mg/5 mg once daily	160 mg/5 mg–320 mg/ 10 mg once daily	$1.71/160 mg/ 10 mg	$51.30		
Other Combination Products							
Amlodipine and valsartan and HCTZ	Exforge HCT	5 mg/160 mg/12.5 mg once daily	10 mg/320 mg/25 mg up to once daily	$5.47/160 mg valsartan	$164.10		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 30, 2020. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
ACE, angiotensin-converting enzyme; ER, extended release; HCTZ, hydrochlorothiazide.

ACE inhibitors are the agents of choice in persons with type 1 diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to end-stage renal disease. Many authorities have expanded this indication to include persons with type 1 and type 2 diabetes mellitus with microalbuminuria who do not meet the usual criteria for antihypertensive therapy. ACE inhibitors may also delay the progression of nondiabetic kidney disease. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that the ACE inhibitor ramipril reduced the number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes and also reduced the incidence of new-onset heart failure, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. Although this was not specifically a hypertensive population, the benefits were associated with a modest reduction in blood pressure, and the results inferentially support the use of ACE inhibitors in similar hypertensive patients. ACE inhibitors are a drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with heart failure with reduced ejection fraction and are indicated also in asymptomatic patients with reduced ejection fraction.

How to initiate therapy—A baseline metabolic panel should be drawn prior to starting medications that interfere with the RAAS, repeated 1–2 weeks after initiation of therapy to evaluate changes in creatinine and potassium. Minor dose adjustments of these medications rarely trigger significant shifts in these values.

Side effects—An advantage of the ACE inhibitors is their relative freedom from troublesome side effects (Table 11–6). Severe hypotension can occur in patients with bilateral renal artery stenosis; significant increases in creatinine may ensue but are usually reversible with the discontinuation of the ACE inhibitor. Hyperkalemia may develop in patients with kidney disease and type IV renal tubular acidosis (commonly seen in patients with diabetes) and in older adults. A chronic dry cough is common, seen in 10% of patients or more, and may require stopping the drug. Skin rashes are observed with any ACE inhibitor. Angioedema is an uncommon but potentially dangerous side effect of all agents of this class because of their inhibition of kininase. Exposure of the fetus to ACE inhibitors during the second and third trimesters of pregnancy has been associated with a variety of defects due to hypotension and reduced renal blood flow.

B. Angiotensin II Receptor Blockers

ARBs can improve cardiovascular outcomes in patients with hypertension as well as in patients with related conditions, such as heart failure and type 2 diabetes with nephropathy. ARBs have not been compared with ACE inhibitors in randomized controlled trials in patients with hypertension, but two trials comparing losartan with captopril in heart failure and post–myocardial infarction left ventricular dysfunction showed trends toward worse outcomes in the losartan group. By contrast, valsartan seems as effective as ACE inhibitors in these settings. Within group heterogeneity of antihypertensive potency and duration of action might explain such observations. The Losartan Intervention for Endpoints (LIFE) trial in nearly 9000 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy—comparing losartan with the beta-blocker atenolol as initial therapy—demonstrated a significant reduction in stroke with losartan. Of note is that in diabetic patients, death and myocardial infarction were also reduced, and there was a lower occurrence of new-onset diabetes. In a subgroup analysis from the LIFE trial, atenolol appeared to be superior to losartan in blacks, while the opposite was the case in non-blacks. A similar lack of efficacy of lisinopril compared to diuretics and calcium channel blockers was observed in blacks in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attach Trial (ALLHAT), suggesting that ACE inhibitors and ARBs may not be the preferred agents in black patients. In the treatment of hypertension, combination therapy with an ACE inhibitor and an ARB is not advised because it generally offers no advantage over monotherapy at maximum dose with addition of a complementary class where necessary.

Side effects—Unlike ACE inhibitors, the ARBs rarely cause cough and are less likely to be associated with skin rashes or angioedema (Table 11–6). However, as seen with ACE inhibitors, hyperkalemia can be a problem, and patients with bilateral renal artery stenosis may exhibit hypotension and worsened kidney function. Olmesartan has been linked to a sprue-like syndrome, presenting with abdominal pain, weight loss, and nausea, which subsides upon drug discontinuation. There is evidence from an observational study suggesting that ARBs and ACE inhibitors are less likely to be associated with depression than calcium channel blockers and beta-blockers.

C. Renin Inhibitors

Since renin cleavage of angiotensinogen is the rate-limiting step in the renin-angiotensin cascade, the most efficient inactivation of this system would be expected with renin inhibition. Conventional ACE inhibitors and ARBs probably offer incomplete blockade, even in combination. Aliskiren, a renin inhibitor, binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen. As a consequence, levels of angiotensins I and II are reduced and renin concentration is increased. Aliskiren effectively lowers blood pressure, reduces albuminuria, and limits left ventricular hypertrophy, but it has yet to be established as a first-line drug based on outcomes data. The combination of aliskiren with ACE inhibitors or ARBs in persons with type 2 diabetes mellitus offers no advantage and might even increase the risk of adverse cardiac or renal consequences.

D. Calcium Channel Blocking Agents

These agents act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other vasodilators. They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension (Table 11–7). For these reasons, they may be preferable to beta-blockers and ACE inhibitors in blacks and older persons. Verapamil and diltiazem should be combined cautiously with beta-blockers because of their potential for depressing atrioventricular (AV) conduction and sinus node automaticity as well as contractility.

Table 11–7. Antihypertensive drugs: calcium channel blocking agents.

Drug	Proprietary Name	Initial Oral Dosage	Dosage Range	Cost of 30 Days of Treatment (Average Dosage)[1]	Special Properties			Adverse Effects	Comments
					Peripheral Vasodilation	Cardiac Automaticity and Conduction	Contractility		
Nondihydropyridine Agents									
Diltiazem	Cardizem SR	90 mg twice daily	180–360 mg in 2 doses	$283.20 (120 mg twice daily)	++	↓↓	↓↓	Edema, headache, bradycardia, GI disturbances, dizziness, AV block, heart failure, urinary frequency.	Also approved for angina.
	Cardizem CD	180 mg ER once daily	180–360 mg ER once daily	$42.00 (240 mg once daily)					
	Cartia XT	180 or 240 mg ER once daily	180–480 mg ER once daily	$42.00 (240 mg once daily)					
	Dilacor XR	180 or 240 mg ER once daily	180–540 mg ER once daily	$42.90 (240 mg once daily)					
	Dilt-CD	180 or 240 mg ER once daily	180–480 mg ER once daily	$39.00 (240 mg once daily)					
	Diltia XT	180 or 240 mg ER once daily	180–540 mg ER once daily	$42.00 (240 mg once daily)					
	Taztia XT	120 or 180 mg ER once daily	120–540 mg ER once daily	$52.80 (240 mg once daily)					
	Tiazac	120 or 240 mg ER once daily	120–540 mg ER once daily	$52.80 (240 mg once daily)					
Verapamil	Calan	80 mg three times daily	80–480 mg in 3 divided doses	$43.20 (80 mg three times daily)	++	↓↓↓	↓↓↓	Same as diltiazem but more likely to cause constipation and heart failure.	Also approved for angina and arrhythmias.
	Calan SR	180 mg ER once daily	180–480 mg ER in 1 or 2 doses	$49.20 (240 mg once daily)					
	Verelan	120 or 240 mg ER once daily	240–480 mg ER once daily	$68.70 (240 mg once daily)					
	Verelan PM	100 or 200 mg ER once daily	100–400 mg ER once daily	$75.90 (200 mg once daily)					
Dihydropyridines									
Amlodipine	Norvasc	2.5 mg once daily	2.5–10 mg once daily	$3.00 (10 mg once daily)	+++	↓/0	↓/0	Edema, dizziness, palpitations, flushing, headache, hypotension, tachycardia, GI disturbances, urinary frequency.	Amlodipine, nicardipine, and nifedipine also approved for angina.
Amlodipine and atorvastatin	Caduet	2.5 mg/10 mg once daily	10 mg/80 mg once daily	$281.10 (10 mg/ 40 mg daily)	+++	↓/0	↓/0	Myopathy, hepatotoxicity, edema with amlodipine and atorvastatin.	
Felodipine	Plendil	5 mg ER once daily	5–10 mg ER once daily	$81.60 (10 mg ER daily)	+++	↓/0	↓/0		
Isradipine	DynaCirc	2.5 mg twice daily	2.5–5 mg twice daily	$120.00 (5 mg twice daily)	+++	↓/0	↓		
Nicardipine	Cardene	20 mg three times daily	20–40 mg three times daily	$200.70 (20 mg three times daily)	+++	↓/0	↓		
Nifedipine	Adalat CC	30 mg ER once daily	30–90 mg ER once daily	$74.40/60 mg daily	+++	↓	↓↓		
	Procardia XL	30 or 60 mg ER once daily	30–120 mg ER once daily	$54.90/60 mg daily					
Nisoldipine	Sular	17 mg daily	17–34 mg daily	$251.70 (34 mg once daily)	+++	↓/0	↓		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 30, 2020. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
AV, atrioventricular; ER, extended release; GI, gastrointestinal.

Initial concerns about possible adverse cardiac effects of calcium channel blockers have been convincingly allayed by several subsequent large studies that have demonstrated that calcium channel blockers are equivalent to ACE inhibitors and thiazide diuretics in prevention of coronary heart disease, major cardiovascular events, cardiovascular death, and total mortality. A protective effect against stroke with calcium channel blockers is well established, and in two trials (ALLHAT and the Systolic Hypertension in Europe trial), these agents appeared to be more effective than diuretic-based therapy.

Side effects—The most common side effects of calcium channel blockers are headache, peripheral edema, bradycardia, and constipation (especially with verapamil in older adults) (Table 11–7). The dihydropyridine agents —nifedipine, nicardipine, isradipine, felodipine, nisoldipine, and amlodipine—are more likely to produce symptoms of vasodilation, such as headache, flushing, palpitations, and peripheral edema. Edema is minimized by coadministration of an ACE inhibitor or ARB. Calcium channel blockers have negative inotropic effects and should be used cautiously in patients with cardiac dysfunction. Amlodipine is the only calcium channel blocker with established safety in patients with severe heart failure.

E. Diuretics

Thiazide diuretics (Table 11–8) are the antihypertensives that have been most extensively studied and most consistently effective in clinical trials. They lower blood pressure initially by decreasing plasma volume, but during long-term therapy, their major hemodynamic effect is reduction of peripheral vascular resistance. Most of the antihypertensive effect of these agents is achieved at lower dosages than used previously (typically, 12.5 mg of hydrochlorothiazide or equivalent), but their biochemical and metabolic effects are dose related. Chlorthalidone has the advantage of better 24-hour blood pressure control than hydrochlorothiazide in clinical trials. Thiazides may be used at higher doses if plasma potassium is above 4.5 mmol/L. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Because of these adverse effects, loop diuretics should be reserved for use in patients with kidney dysfunction (serum creatinine greater than 2.5 mg/dL [208.3 mcmol/L]; estimated glomerular filtration rate [eGFR] less than 30 mL/min) in which case they are more effective than thiazides. Relative to beta-blockers and ACE inhibitors, diuretics are more potent in blacks, older individuals, the obese, and other subgroups with increased plasma volume or low plasma renin activity (or both). They are relatively more effective in smokers than in nonsmokers. Long-term thiazide administration also mitigates the loss of bone mineral content in older women at risk for osteoporosis.

Table 11–8. Antihypertensive drugs: diuretics (in descending order of preference).

Drugs	Proprietary Names	Initial Oral Doses	Dosage Range	Cost per Unit	Cost of 30 Days of Treatment[1] (Average Dosage)	Adverse Effects	Comments
Thiazides and Related Diuretics							
Hydrochloro-thiazide (HCTZ)	Esidrix, Microzide	12.5 or 25 mg once daily	12.5–50 mg once daily	$0.05/25 mg	$1.50	$\downarrow$K+, $\downarrow$Mg^{2+}, $\uparrow$Ca^{2+}, $\downarrow$Na+, $\uparrow$uric acid, $\uparrow$glucose, $\uparrow$LDL cholesterol, $\uparrow$triglycerides; rash, erectile dysfunction.	Low dosages effective in many patients without associated metabolic abnormalities; metolazone more effective with concurrent kidney disease; indapamide does not alter serum lipid levels.
Chlorthalidone	Thalitone	12.5 or 25 mg once daily	12.5–50 mg once daily	$1.21/25 mg	$36.30		Chlorthalidone: better 24-hour blood pressure control than HCTZ because of longer half-life
Metolazone	Zaroxolyn	1.25 or 2.5 mg once daily	1.25–5 mg once daily	$1.51/5 mg	$45.30		
Indapamide	Lozol	2.5 mg once daily	2.5–5 mg once daily	$0.83/2.5 mg	$24.90		
Bendroflume-thiazide	Aprinox Neo-Naclex	2.5 mg once daily	—	—	—	—	Not available in United States
Loop Diuretics							
Furosemide	Lasix	20 mg twice daily	40–320 mg in 2 or 3 doses	$0.16/40 mg	$9.60	Same as thiazides, but higher risk of excessive diuresis and electrolyte imbalance. Increases calcium excretion.	Furosemide: Short duration of action a disadvantage; should be reserved for patients with kidney disease or fluid retention. Poor antihypertensive.
Ethacrynic acid	Edecrin	50 mg once daily	50–100 mg once or twice daily	$23.95/25 mg	$1437.00		
Bumetanide	(generic)	0.25 mg twice daily	0.5–10 mg in 2 or 3 doses	$0.54/1 mg	$32.40		
Torsemide	Demadex	5 mg once daily	5–10 mg once daily	$0.70/10 mg	$21.00		Torsemide: Effective blood pressure medication at low dosage.
Aldosterone Receptor Blockers							
Spironolactone	Aldactone	12.5 or 25 mg once daily	12.5–100 mg once daily	$0.19/25 mg	$5.70	Hyperkalemia, metabolic acidosis, gynecomastia.	Can be useful add-on therapy in patients with refractory hypertension.
Amiloride	(generic)	5 mg once daily	5–10 mg once daily	$1.25/5 mg	$37.50		
Eplerenone	Inspra	25 mg once daily	25–100 mg once daily	$4.10/25 mg	$123.00		
Combination Products							
HCTZ and triamterene	Dyazide, Max-zide-25 (25/37.5 mg)	1 tab once daily	1 or 2 tabs once daily	$0.27	$8.10	Same as thiazides plus GI disturbances, hyperkalemia rather than hypokalemia, headache; triamterene can cause kidney stones and kidney dysfunction; spironolactone causes gynecomastia. Hyperkalemia can occur if this combination is used in patients with advanced kidney disease or those taking ACE inhibitors.	Use should be limited to patients with demonstrable need for a potassium-sparing agent.
HCTZ and amiloride	(generic) (50/5 mg)	½ tab once daily	1 or 2 tabs once daily	$1.16	$34.80		
HCTZ and spironolactone	Aldactazide (25/25 mg; 50/50 mg)	1 tab (25/25 mg) once daily	1–4 tabs once daily	$1.24/(25/25 mg)	$37.20		

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 30, 2020. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
ACE, angiotensin-converting enzyme; GI, gastrointestinal; LDL, low-density lipoprotein.

Overall, diuretics administered alone control blood pressure in 50% of patients with mild to moderate hypertension and can be used effectively in combination with all other agents. They are also useful for lowering isolated or predominantly systolic hypertension.

Side effects—The adverse effects of diuretics relate primarily to the metabolic changes listed in Table 11–8. Erectile dysfunction, skin rashes, and photosensitivity are less frequent. Hypokalemia has been a concern but is uncommon at the recommended dosages. The risk can be minimized by limiting dietary salt or increasing dietary potassium; potassium replacement is not usually required to maintain serum K$^+$ at greater than 3.5 mmol/L. Higher serum K+ levels are prudent in patients at special risk from intracellular potassium depletion, such as those taking digoxin or with a history of ventricular arrhythmias in which case a potassium-sparing agent could be used. Compared with ACE inhibitors and ARBs, diuretic therapy is associated with a slightly higher incidence of mild new-onset diabetes. Diuretics also increase serum uric acid and may precipitate gout. Increases in blood glucose, triglycerides, and LDL cholesterol may occur but are relatively minor during long-term low-dose therapy. The potential for worsening of diabetes is outweighed by the advantages of blood pressure control, and diuretics should not be withheld from

diabetic patients.

F. Aldosterone Receptor Antagonists

Spironolactone and eplerenone are natriuretic in sodium-retaining states, such as heart failure and cirrhosis, but only very weakly so in hypertension. These drugs have reemerged in the treatment of hypertension, particularly in resistant patients and are helpful additions to most other antihypertensive medications. Consistent with the increasingly appreciated importance of aldosterone in essential hypertension, the aldosterone receptor blockers are effective at lowering blood pressure in all hypertensive patients regardless of renin level, and are also effective in blacks. Aldosterone plays a central role in target-organ damage, including the development of ventricular and vascular hypertrophy and renal fibrosis. Aldosterone receptor antagonists ameliorate these consequences of hypertension, to some extent independently of effects on blood pressure.

Side effects—Spironolactone can cause breast pain and gynecomastia in men through activity at the progesterone receptor, an effect not seen with the more specific eplerenone. Hyperkalemia is a problem with both drugs, chiefly in patients with chronic kidney disease. Hyperkalemia is more likely if the pretreatment plasma potassium exceeds 4.5 mmol/L.

G. Beta-Adrenergic Blocking Agents

These drugs are effective in hypertension because they decrease the heart rate and cardiac output. The beta-blockers also decrease renin release and are more efficacious in populations with elevated plasma renin activity, such as younger white patients. They neutralize the reflex tachycardia caused by vasodilators and are especially useful in patients with associated conditions that benefit from the cardioprotective effects of these agents. These include individuals with angina pectoris, previous myocardial infarction, and stable heart failure as well as those with migraine headaches and somatic manifestations of anxiety.

Although all beta-blockers appear to be similar in antihypertensive potency, they differ in a number of pharmacologic properties (these differences are summarized in Table 11–9), including specificity to the cardiac beta-1-receptors (cardioselectivity) and whether they also block the beta-2-receptors in the bronchi and vasculature*; at higher dosages, however, all agents are nonselective.* The beta-blockers also differ in their pharmacokinetics, lipid solubility—which determines whether they cross the blood-brain barrier predisposing to central nervous system side effects—and route of metabolism. Metoprolol reduces mortality and morbidity in patients with chronic stable heart failure with reduced ejection fraction (see Chapter 10). Carvedilol and nebivolol maintain cardiac output and are beneficial in patients with left ventricular systolic dysfunction. Carvedilol and nebivolol may reduce peripheral vascular resistance by concomitant alpha-blockade (carvedilol) and increased nitric oxide release (nebivolol). Because of the lack of efficacy in primary prevention of myocardial infarction and inferiority compared with other drugs in prevention of stroke and left ventricular hypertrophy, traditional beta-blockers should not be used as first-line agents in the treatment of hypertension without specific compelling indications (such as active coronary artery disease). Vasodilating beta-blockers may emerge as alternative first-line antihypertensives, but this possibility has yet to be rigorously tested in outcome studies.

Table 11–9. Antihypertensive drugs: beta-adrenergic blocking agents.

Drug	Proprietary Name	Initial Oral Dosage	Dosage Range	Cost per Unit	Cost of 30 Days of Treatment (Based on Average Dosage)[1]	Beta-1 Selectivity[2]	ISA[3]	MSA[4]	Lipid Solubility	Renal vs Hepatic Elimination	Comments[5]
Acebutolol	Sectral	400 mg once daily	200–1200 mg in 1 or 2 doses	$1.57/400 mg	$47.10	+	+	+	+	H > R	Positive ANA; rare LE syndrome; also indicated for arrhythmias. Doses > 800 mg have beta-1 and beta-2 effects.
Atenolol	Tenormin	25 mg once daily	25–100 mg once daily	$0.79/50 mg	$23.70	+	0	0	0	R	Also indicated for angina and post-MI. Doses > 100 mg have beta-1 and beta-2 effects.
Atenolol/ chlorthali- done	Tenoretic	50 mg/25 mg once daily	50 mg/25 mg–100 mg/ 25 mg once daily	$1.88/50 mg/ 25 mg	$56.40	+	0	0	0	R	
Betaxolol	Kerlone	10 mg once daily	10–40 mg once daily	$0.78/10 mg	$23.40	+	0	0	+	H > R	
Bisoprolol	Zebeta	5 mg once daily	5–20 mg once daily	$1.22/10 mg	$36.60	+	0	0	0	R = H	Also effective for heart failure.
Bisoprolol and HCTZ	Ziac	2.5 mg/6. 25 mg once daily	2.5 mg/ 6.25 mg–10 mg/ 6.25 mg once daily	$1.14/2.5/ 6.25 mg	$34.20	+	0	0	0	R = H	Low-dose combination approved for initial therapy.
Carvedilol	Coreg Coreg CR	6.25 mg twice daily 20 mg ER once daily	12.5–50 mg in 2 doses 20–80 mg ER once daily	$0.09/25 mg $9.91/any tablet	$5.40 (25 mg twice a day) $297.30	0	0	0	+++	H > R	Alpha:beta blocking activity 1:9; may cause orthostatic symp- toms; effective for heart failure. Nitric oxide potentiating vasodi- latory activity.
Labetalol	Trandate	100 mg twice daily	200–2400 mg in 2 doses	$0.39/200 mg	$23.40	0	0/+	0	++	H	Alpha:beta blocking activity 1:3; more orthostatic hypotension, fever, hepatotoxicity.
Metoprolol	Lopressor Toprol-XL (SR prepara- tion)	50 mg twice daily 25 mg once daily	50–200 mg twice daily 25–400 mg once daily	$0.03/50 mg $0.31/100 mg	$1.80 $9.30	+	0	+	+++	H	Also indicated for angina and post-MI. Approved for heart failure. Doses > 100 mg have beta-1 and beta-2 effects.
Metoprolol and HCTZ	Lopressor HCT	50 mg/12.5 mg twice daily	50 mg/25 mg–200 mg/ 50 mg	$1.63/100 mg/ 25 mg	$97.80	+	0	+	+++	H	
Nadolol	Corgard	20 mg once daily	20–320 mg once daily	$3.96/40 mg	$118.80	0	0	0	0	R	
Nadolol and bendroflu- methazide	Corzide	40 mg/5 mg once daily	40 mg/5 mg–80 mg/ 5 mg once daily	6.14/80 mg/ 5 mg	$184.20						
Nebivolol	Bystolic	5 mg once daily	40 mg once daily	$6.02/5 mg	$180.60	+	0	0	++	H	Nitric oxide potentiating vasodila- tory activity.
Pindolol	Visken	5 mg twice daily	10–60 mg in 2 doses	$1.10/5 mg	$66.00	0	++	+	+	H > R	In adults, 35% renal clearance.
Propranolol	Inderal Inderal LA InnoPran XL	20 mg twice daily 80 mg ER once daily 80 mg ER once nightly	40–640 mg in 2 doses 120–640 mg ER once daily 80–120 mg ER once nightly	$0.65/40 mg $1.92/120 mg $30.20/ 120 mg	$39.00 $57.60 $906.00	0	0	++	+++	H	Also indicated for angina and post-MI.
Propranolol and HCTZ	(generic)	40 mg/25 mg twice daily	80 mg/25 mg twice daily	$1.41/80 mg/25 mg	$84.60	0	0	++	+++	H	
Timolol	(generic)	5 mg twice daily	10–60 mg in 2 doses	$1.70/10 mg	$102.00	0	0	0	++	H > R	Also indicated for post-MI; 80% hepatic clearance.

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 30, 2020. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
[2]Agents with beta-1 selectivity are less likely to precipitate bronchospasm and decrease peripheral blood flow in low doses, but selectivity is only relative.
[3]Agents with ISA cause less resting bradycardia and lipid changes.
[4]MSA generally occurs at concentrations greater than those necessary for beta-adrenergic blockade. The clinical importance of MSA by beta-blockers has not been defined.
[5]Adverse effects of all beta-blockers: bronchospasm, fatigue, sleep disturbance and nightmares, bradycardia and atrioventricular block, worsening of heart failure, cold extremities, gastrointestinal distur- bances, erectile dysfunction, $\uparrow$ triglycerides, $\downarrow$ high-density lipoprotein cholesterol, rare blood dyscrasias.
ANA, antinuclear antibody; ER, extended release; HCTZ, hydrochlorothiazide; ISA, intrinsic sympathomimetic activity; LE, lupus erythematosus; MI, myocardial infarction; MSA, membrane-stabilizing activ- ity; SR, sustained release; 0, no effect; +, some effect; ++, moderate effect; +++, most effect.

Side effects—The side effects of beta-blockers include inducing or exacerbating bronchospasm in predisposed patients; sinus node dysfunction and AV conduction depression (resulting in bradycardia or AV block); nasal congestion; Raynaud phenomenon; and central nervous system symptoms with nightmares, excitement, depression, and confusion. Fatigue, lethargy, and erectile dysfunction may occur. The traditional beta-blockers (but not the vasodilator beta-blockers carvedilol and nebivolol) have an adverse effect on lipids and glucose metabolism. Beta-blockers are used cautiously in patients with type 1 diabetes, since they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeogenesis. These drugs should also be used with caution in patients

with advanced peripheral vascular disease associated with rest pain or nonhealing ulcers, but they are generally well tolerated in patients with mild claudication. Nebivolol can be safely used in patients with stage II claudication (claudication at 200 m).

In treatment of pheochromocytoma, beta-blockers should not be administered until alpha-blockade (eg, phentolamine) has been established. Otherwise, blockade of vasodilatory beta-2-adrenergic receptors will allow unopposed vasoconstrictor alpha-adrenergic receptor activation with worsening of hypertension. *For the same reason, beta-blockers should not be used to treat hypertension arising from cocaine use.*

Great care should be exercised if the decision is made, in the absence of compelling indications, to remove beta-blockers from the treatment regimen because abrupt withdrawal can precipitate acute coronary events and severe increases in blood pressure.

H. Alpha-Adrenoceptor Antagonists

Prazosin, terazosin, and doxazosin (Table 11–10) block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance. These agents are effective as single-drug therapy in some individuals, but tachyphylaxis may appear during long-term therapy. Unlike beta-blockers and diuretics, alpha-blockers have no adverse effect on serum lipid levels. In fact, alpha-blockers increase HDL cholesterol while reducing total cholesterol; whether this is beneficial in the long term has not been established.

Table 11–10. Alpha-adrenoceptor blocking agents, sympatholytics, and vasodilators.

Drug	Proprietary Names	Initial Dosage	Dosage Range	Cost per Unit	Cost of 30 Days of Treatment (Average Dosage)[1]	Adverse Effects	Comments
Alpha-Adrenoceptor Blockers							
Doxazosin	Cardura Cardura XL	1 mg at bedtime 4 mg ER once daily	1–16 mg once daily 4–8 mg ER once daily	$0.29/4 mg $6.74/4 mg ER	$8.70 (4 mg once daily) $202.20 (4 mg ER once daily)	Syncope with first dose; postural hypotension, dizziness, palpitations, headache, weakness, drowsiness, sexual dysfunction, anticholinergic effects, urinary incontinence; first-dose effects may be less with doxazosin.	May ↑ HDL and ↓ LDL cholesterol. May provide short-term relief of obstructive prostatic symptoms. Less effective in preventing cardiovascular events than diuretics.
Prazosin	Minipress	1 mg at bedtime	2–20 mg in 2 or 3 doses	$0.95/5 mg	$57.00 (5 mg twice daily)		
Terazosin	Hytrin	1 mg at bedtime	1–20 mg in 1 or 2 doses	$1.60/1, 2, 5, 10 mg	$48.00 (5 mg once daily)		
Central Sympatholytics							
Clonidine	Catapres Catapres TTS (transdermal patch)	0.1 mg twice daily 0.1 mg/day patch weekly	0.2–0.6 mg in 2 doses 0.1–0.3 mg/day patch weekly	$0.21/0.1 mg $55.77/0.2 mg patch	$12.60 (0.1 mg twice daily) $223.08 (0.2 mg weekly)	Sedation, dry mouth, sexual dysfunction, headache, bradyarrhythmias; side effects may be less with guanfacine. Contact dermatitis with clonidine patch. Methyldopa also causes hepatitis, hemolytic anemia, fever.	"Rebound" hypertension may occur even after gradual withdrawal.
Clonidine and chlorthalidone	Clorpres	0.1 mg/15 mg one to three times daily	0.1 mg/15 mg–0.3 mg/15 mg	$2.77/0.1 mg/15 mg	$166.20/0.1 mg/ 15 mg twice daily		
Guanfacine	Tenex	1 mg once daily	1–3 mg once daily	$0.87/1 mg	$26.10 (1 mg once daily)		
Methyldopa	Aldochlor	250 mg twice daily	500–2000 mg in 2 doses	$0.66/500 mg	$39.60 (500 mg twice daily)		Methyldopa should be avoided in favor of safer agents.
Peripheral Neuronal Antagonists							
Reserpine	(generic)	0.05 mg once daily	0.05–0.25 mg once daily	$1.19/0.1 mg	$35.70 (0.1 mg once daily)	Depression (less likely at low dosages, ie, < 0.25 mg), night terrors, nasal stuffiness, drowsiness, peptic disease, GI disturbances, bradycardia.	
Direct Vasodilators							
Hydralazine	Apresoline	25 mg twice daily	50–300 mg in 2–4 doses	$0.15/25 mg	$9.00 (25 mg twice daily)	GI disturbances, tachycardia, headache, nasal congestion, rash, LE-like syndrome.	May worsen or precipitate angina.
Minoxidil	(generic)	5 mg once daily	10–40 mg once daily	$1.28/10 mg	$38.40 (10 mg once daily)	Tachycardia, fluid retention, headache, hirsutism, pericardial effusion, thrombocytopenia.	Should be used in combination with beta-blocker and diuretic.

[1]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.
Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at https://www.micromedexsolutions.com, accessed March 30, 2020. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.
ER, extended release; GI, gastrointestinal; LE, lupus erythematosus.

Side effects—Side effects are relatively common (Table 11–10). These include marked hypotension after the first dose which, therefore, should be small and given at bedtime. Post-dosing palpitations, headache, and nervousness may continue to occur during long-term therapy; these symptoms may be less frequent or severe with doxazosin because of its more gradual onset of action. In ALLHAT, persons receiving doxazosin as initial therapy had a significant increase in heart failure hospitalizations and a higher incidence of stroke relative to those receiving diuretics, prompting discontinuation of this arm of the study. Cataractectomy in patients exposed to alpha-blockers can be complicated by the floppy iris syndrome, even after discontinuation of the drug, so the ophthalmologist should be alerted that the patient has been taking the drug prior to surgery.

To summarize, alpha-blockers should generally not be used as initial agents to treat hypertension—except perhaps in men with symptomatic prostatism or nightmares linked to posttraumatic stress disorder.

I. Drugs With Central Sympatholytic Action

Methyldopa, clonidine, guanabenz, and guanfacine (Table 11–10) lower blood pressure by stimulating alpha-adrenergic receptors in the central nervous system, thus reducing efferent peripheral sympathetic outflow. There is

considerable experience with methyldopa in pregnant women, and it is still used for this population. Clonidine is available in patches, which may have particular value in noncompliant patients. All of these central sympatholytic agents are effective as single therapy in some patients, but they are usually used as second- or third-line agents because of the high frequency of drug intolerance.

Side effects—Side effects include sedation, fatigue, dry mouth, postural hypotension, and erectile dysfunction. An important concern is rebound hypertension following withdrawal. Methyldopa also causes hepatitis and hemolytic anemia and should be restricted to individuals who have already tolerated long-term therapy.

J. Peripheral Sympathetic Inhibitors

These agents are now used infrequently and usually in refractory hypertension. Reserpine remains a cost-effective antihypertensive agent (Table 11–10). Its reputation for inducing mental depression and its other side effects— sedation, nasal stuffiness, sleep disturbances, and peptic ulcers—has made it unpopular, though these problems are uncommon at low dosages. Guanethidine and guanadrel inhibit catecholamine release from peripheral neurons but frequently cause orthostatic hypotension (especially in the morning or after exercise), diarrhea, and fluid retention.

K. Arteriolar Dilators

Hydralazine and minoxidil (Table 11–10) relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia; increase myocardial contractility; and cause headache, palpitations, and fluid retention. To counteract these effects, the agents are usually given in combination with diuretics and beta-blockers in resistant patients. Hydralazine produces frequent gastrointestinal disturbances and may induce a lupus-like syndrome. Minoxidil causes hirsutism and marked fluid retention; this very potent agent is reserved for the most refractory of cases.

Antihypertensive Medications & the Risk of Cancer

A number of observational studies have examined the association between long-term exposure to antihypertensive medications and cancer. Weak associations have been suggested by some of these studies, but results have been very mixed. Examples of positive studies include an association between ACE inhibitors and lung cancer (hazard ratio 1.14) and between photosensitizing drugs and squamous skin cancer (the use of alpha-2-receptors blockers and diuretics was associated with a 17% increased risk of squamous cell cancer). The relationship between calcium channel blockers and breast cancer remains uncertain. In the absence of large-scale prospective studies with cancer as a prespecified outcome measure, the effect of antihypertensive drugs on the risk of cancer remains uncertain. By contrast, the beneficial effect of these drugs on cardiovascular outcomes has been clearly established. Concern about increased risk of cancer should not be minimized, but at present there are no compelling data to prompt a change in prescribing patterns.

Hicks BM et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018 Oct 24;363:k4209. [PMID: 30355745]

Ostrov DA et al. Rationally designed small molecules to prevent type 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2019 Apr;26(2):90–5. [PMID: 30694829]

Su KA et al. Photosensitizing antihypertensive drug use and risk of cutaneous squamous cell carcinoma. Br J Dermatol. 2018 Nov;179(5):1088–94. [PMID: 29723931]

Wright CM et al. Calcium channel blockers and breast cancer incidence: an updated systematic review and meta-analysis of the evidence. Cancer Epidemiol. 2017 Oct;50(Pt A):113–24. [PMID: 28866282]

Developing an Antihypertensive Regimen

Historically, data from large placebo-controlled trials supported the overall conclusion that antihypertensive therapy with diuretics and beta-blockers had a major beneficial effect on a broad spectrum of cardiovascular outcomes, reducing the incidence of stroke by 30–50% and of heart failure by 40–50%, and halting progression to accelerated hypertension syndromes. The decreases in fatal and nonfatal coronary heart disease and cardiovascular and total mortality were less dramatic, ranging from 10% to 15%. Similar placebo-controlled data pertaining to the newer agents are generally lacking, except for stroke reduction with the calcium channel blocker nitrendipine in the

Systolic Hypertension in Europe trial. However, there is substantial evidence that ACE inhibitors, and to a lesser extent ARBs, reduce adverse cardiovascular outcomes in other related populations (eg, patients with diabetic nephropathy, heart failure, or postmyocardial infarction and individuals at high risk for cardiovascular events). Most large clinical trials that have compared outcomes in relatively unselected patients have failed to show a difference between newer agents—such as ACE inhibitors, calcium channel blockers, and ARBs—and the older diuretic-based regimens with regard to survival, myocardial infarction, and stroke. Where differences have been observed, they have mostly been attributable to subtle asymmetries in blood pressure control rather than to any inherent advantages of one agent over another. Recommendations for initial treatment identify ACE inhibitors, ARBs, and calcium channel blockers as valid choices. Because of their adverse metabolic profile, initial therapy with thiazides might best be restricted to older patients. Thiazides are acceptable as first-line therapy in blacks because of specific efficacy in this group.

As discussed above, beta-blockers are not ideal first-line drugs in the treatment of hypertension without compelling indications for their use (such as active coronary artery disease and heart failure). Vasodilator beta-blockers (such as carvedilol and nebivolol) may produce better outcomes than traditional beta-blockers; however, this possibility remains a theoretical consideration.

The American Diabetes Association has advocated evening dosing of one or more antihypertensive medications to restore nocturnal blood pressure dipping. Outcomes data to support this proposal are limited. The Spanish MAPEC study of such nocturnal antihypertensive dosing showed a significant reduction in a range of major cardiovascular events in 2156 participants over 5.6 years. However, there are concerns that ischemic optic neuropathy may be triggered by profound nocturnal hypotension. Thus, larger studies are necessary before this approach can be firmly recommended.

Drugs that interrupt the renin-angiotensin cascade are more effective in young, white persons, in whom renin tends to be higher. Calcium channel blockers and diuretics are more effective in older or black persons, in whom renin levels are generally lower. Many patients require two or more medications and even then a substantial proportion fail to achieve the goal blood pressure. A stepped care approach to the drug treatment of hypertension is outlined in Table 11–11. In diabetic patients, three or four drugs are usually required to reduce systolic blood pressure to less than 140 mm Hg. In many patients, blood pressure cannot be adequately controlled with any combination. As a result, debating the appropriate first-line agent is less relevant than determining the most appropriate combinations of agents. The mnemonic ABCD can be used to remember four classes of antihypertensive medications. These four classes can be divided into two categories: AB and CD. AB refers to drugs that block the RAAS (**A**CE/ARB and **b**eta-blockers). CD refers to those that work in other pathways (**c**alcium channel blockers and **d**iuretics). As discussed above, beta-blockers are no longer considered first-line drugs in the absence of compelling indications. Combinations of drugs between the two categories are more potent than combinations from within a category. Many experts recommend the use of fixed-dose combination (between two categories) antihypertensive agents as first-line therapy in patients with substantially elevated systolic pressures (greater than 160/100 mm Hg) or difficult-to-control hypertension (which is often associated with diabetes or kidney dysfunction). In light of unwanted metabolic effects, calcium channel blockers might be preferable to thiazides in the younger hypertensive patient requiring a second antihypertensive drug following initiation of therapy with an ACE inhibitor or ARB. Furthermore, based on the results from the ACCOMPLISH trial, a combination of ACE inhibitor and calcium channel blocker may also prove optimal for patients at high risk for cardiovascular events. The initial use of low-dose combinations allows faster blood pressure reduction without substantially higher intolerance rates and is likely to be better accepted by patients. Data from the ALTITUDE study (in patients with type 2 diabetes and chronic kidney disease or cardiovascular disease or both) indicate that the addition of aliskiren to either ARB or ACE inhibitor was associated with worse outcomes and cannot be recommended, at least in this population. A suggested approach to treatment, tailored to patient demographics, is outlined in Table 11–12.

Table 11–11. A step care approach to the initiation and titration of antihypertension medications.[1,2]

Step 1	ACE inhibitor/ARB **or**[3] Calcium channel blocker **or** Thiazide diuretic[4]
Step 2	ACE inhibitor/ARB **plus** Calcium channel blocker **or** thiazide diuretic[5]
Step 3	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic
Step 4	ACE inhibitor/ARB **plus** calcium channel blocker **plus** thiazide diuretic **plus** spironolactone[6]

[1]Allow 2 weeks to reach full effect of each drug. Proceed through steps until target blood pressure is attained.
[2]Beta-blockers can be used at any stage if specifically indicated, eg, heart failure or angina.
[3]The European guidelines recommend starting with low-dose combination of two antihypertensive drugs. American guidelines suggest initiation with dual therapy for stage 2 hypertension, > 160/100 mm Hg.
[4]Thiazide or calcium channel blocker is more effective initial therapy in older people and blacks.
[5]If required, add a calcium channel blocker rather than diuretic in younger patients to avoid long-term exposure to metabolic side effects of diuretics.
[6]Alternatives to spironolactone include eplerenone, amiloride, or triamterene. Watch for hyperkalemia, especially if also receiving ACE inhibitor/ARB. Avoid potassium-sparing diuretics in advanced CKD. If more than three drugs are required at maximum dose, consider specialist referral.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

Table 11–12. Choice of antihypertensive agent based on demographic considerations.[1,2]

	Black, All Ages	All Others, Age < 55 Years	All Others, Age > 55 Years
First-line	CCB or diuretic	ACE inhibitor or ARB[3] or CCB or diuretic[4]	CCB or diuretic[5]
Second-line	ARB[3] or ACE inhibitor[6] or vasodilating beta-blocker[6]	Vasodilating beta-blocker	ACE inhibitor or ARB[3] or vasodilating beta-blocker[7]
Resistant hypertension	Aldosterone receptor blocker	Aldosterone receptor blocker	Aldosterone receptor blocker
Additional options	Centrally acting alpha-agonist or peripheral alpha-antagonist[8]	Centrally acting alpha-agonist or peripheral alpha-antagonist[8]	Centrally acting alpha-agonist or peripheral alpha-antagonist[8]

[1]Compelling indications may alter the selection of an antihypertensive drug.
[2]Start with full dose of one agent, or lower doses of combination therapy. In stage 2 hypertension, consider initiating therapy with a fixed dose combination.
[3]Women of childbearing age should avoid ACE inhibitors and ARBs or discontinue as soon as pregnancy is diagnosed.
[4]The adverse metabolic effects of thiazide diuretics and beta-blockers should be considered in younger patients but may be less important in the older patient.
[5]For patients with significant kidney dysfunction, use loop diuretic instead of thiazide.
[6]Despite the elevated risk of angioedema and cough in blacks, ACE inhibitors are generally well tolerated and are a useful adjunct.
[7]There are theoretical advantages in the use of vasodilating beta-blockers such as carvedilol and nebivolol.
[8]Alpha-antagonists may precipitate or exacerbate orthostatic hypotension in older adults.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

In sum, as a prelude to treatment, the patient should be informed of common side effects and the need for diligent compliance. In patients with mild or stage 1 hypertension (less than 160/90 mm Hg) in whom pharmacotherapy is indicated, treatment should start with a single agent or two-drug combination at a low dose. Follow-up visits should usually be at 4- to 6-week intervals to allow for full medication effects to be established (especially with diuretics) before further titration or adjustment. If, after titration to usual doses, the patient has shown a discernible but incomplete response and a good tolerance of the initial drug, another medication should be added. See Goals of Treatment, above. As a rule of thumb, a blood pressure reduction of 10 mm Hg can be expected for each antihypertensive agent added to the regimen and titrated to the optimum dose. In those with more severe hypertension (stage 2), or with comorbidities (such as diabetes) that are likely to render them resistant to treatment, initiation with combination therapy is advised and more frequent follow-up is indicated.

Patients who are compliant with their medications and who do not respond to conventional combination regimens should usually be evaluated for secondary hypertension before proceeding to more complex regimens.

Medication Nonadherence

Adherence to antihypertensive treatment is alarmingly poor. In one European study of patients' antihypertensive medication compliance, there was a 40% discontinuation rate at 1 year after initiation. Only 39% of patients were found to be taking their medications continuously over a 10-year period. Collaborative care, using clinicians, pharmacists, social workers, and nurses to encourage compliance, has had a variable and often rather modest effect on blood pressure control. Adherence is enhanced by patient education and by use of home blood pressure measurement. The choice of antihypertensive medication is important. Better compliance has been reported for patients whose medications could be taken once daily or as combination pills. Adherence is best with ACE inhibitors and ARBs, and worse with beta-blockers and diuretics.

Consideration of Gender in Hypertension

Because of the preponderance of male recruitment into large-scale clinical trials, the impact of gender on the evaluation and management of hypertension remains uncertain. The limited data that exist suggest a steeper relationship in women between 24-hour ambulatory and night time systolic blood pressure and the risk of cardiovascular events. There are many gender-specific effects on the mechanisms and end organ impact of hypertension. In younger adults, men are more likely to be hypertensive than women, a relationship that reverses in later life. Regression of left ventricular hypertrophy in response to ACE inhibitors is less pronounced in women. Women are more likely to have isolated systolic hypertension, probably because they develop more active left ventricular systolic function and greater vascular stiffness than men. Fibromuscular dysplasia of the renal artery is much more common in women than men. The side effects of many antihypertensive drugs are more pronounced in women than men, including ACE inhibitor–associated cough and hyponatremia and hypokalemia in response to diuretics. Conversely, thiazides can help preserve bone density. Dependent edema due to amlodipine is more likely in women, and women are more sensitive to beta-blockers. There are no data to support a different blood pressure target in women, but this question has not been examined in dedicated clinical trials.

Special Considerations in the Treatment of Diabetic Hypertensive Patients

Hypertensive patients with diabetes are at particularly high risk for cardiovascular events. Data from the ACCORD study of diabetic patients demonstrated that most of the benefits of blood pressure lowering were seen with a systolic target of less than 140 mm Hg. Although there was a reduction in stroke risk at a systolic target below 120/70 mm Hg, treatment to this lower target was associated with an *increased* risk of serious adverse effects. US and Canadian guidelines recommend a blood pressure goal of less than 130/80 mm Hg in diabetic patients. Because of the beneficial effects of ACE inhibitors in diabetic nephropathy, they should be part of the initial treatment regimen. ARBs or perhaps renin inhibitors may be substituted in those intolerant of ACE inhibitors. While the ONTARGET study showed that combinations of ACE inhibitors and ARBs in persons with atherosclerosis or type 2 diabetes with end-organ damage appeared to minimize proteinuria, this strategy slightly increased the risks of progression to dialysis and of death; thus, it is not recommended. Most diabetic patients require combinations of three to five agents to achieve target blood pressure, usually including a diuretic and a calcium channel blocker or beta-blocker. In addition to rigorous blood pressure control, treatment of persons with diabetes should include aggressive treatment of other risk factors.

Treatment of Hypertension in Chronic Kidney Disease

Hypertension is present in 40% of patients with a GFR of 60–90 mL/min, and 75% of patients with a GFR less than 30 mL/min. The rate of progression of chronic kidney disease is markedly slowed by treatment of hypertension. In the SPRINT trial, the reduction in cardiovascular risk associated with lower blood pressure targets was also observed in the subgroup with a GFR of less than 60 mL/min. However, an effect of *lower* blood pressure targets on the slowing of chronic kidney disease progression appears to be restricted to those with pronounced proteinuria. In the SPRINT trial, the lower blood pressure goal was associated with increased risk of acute kidney injury, but this was generally reversible and not associated with elevated biomarkers for ischemic injury. Most experts recommend a blood pressure target of less than 130/80 mm Hg in patients with chronic kidney disease, with consideration of more intensive lowering if proteinuria greater than 1 g per 24 hours is present. Medications that interrupt the renin-angiotensin cascade can slow the progression of kidney disease and are preferred for initial therapy, especially in those with albuminuria of greater than 300 mg/g creatinine. Transition from thiazide to loop diuretic is often necessary to control volume expansion as the eGFR falls below 30 mL/min. ACE inhibitors remain protective and safe in kidney disease associated with significant proteinuria and serum creatinine as high as 5 mg/dL (380

mcmol/L). However, the use of drugs blocking the RAAS cascade in patients with advanced chronic kidney disease should be supervised by a nephrologist. Kidney function and electrolytes should be measured 1 week after initiating treatment and subsequently monitored carefully in patients with kidney disease. An increase in creatinine of 20–30% is acceptable and expected; more exaggerated responses suggest the possibility of renal artery stenosis or volume contraction. Although lower blood pressure levels are associated with acute decreases in GFR, this appears not to translate into an increased risk of developing end-stage renal disease in the long term. Persistence with ACE inhibitor or ARB therapy as the serum potassium level exceeds 5.5 mEq/L is probably not warranted, since other antihypertensive medications are renoprotective as long as goal blood pressures are maintained. However, diuretics can often be helpful in controlling mild hyperkalemia, and there are novel cation exchange polymers (such as patiromer) that sequester potassium in the gut and are more effective and better tolerated than sodium polystyrene sulfonate.

Hypertension Management in Blacks

Substantial evidence indicates that blacks are not only more likely to become hypertensive and more susceptible to the cardiovascular and renal complications of hypertension—they also respond differently to many antihypertensive medications. The REGARDS study illustrates these differences. At systolic blood pressures less than 120 mm Hg, black and white participants between 45 and 64 years of age had equal risk of stroke. For a 10 mm Hg increase in systolic blood pressure, the risk of stroke was threefold higher in black participants. At the level of stage 1 hypertension, the hazard ratio for stroke in black compared to white participants between 45 and 64 years of age was 2.35. This increased susceptibility may reflect genetic differences in the cause of hypertension or the subsequent responses to it, differences in occurrence of comorbid conditions such as diabetes or obesity, or environmental factors such as diet, activity, stress, or access to health care services. In any case, as in all persons with hypertension, a multifaceted program of education and lifestyle modification is warranted. Early introduction of combination therapy has been advocated, but there are no clinical trial data to support a lower than usual blood pressure goal in blacks. Because it appears that ACE inhibitors and ARBs—in the absence of concomitant diuretics—are less effective in blacks than in whites, initial therapy should generally be a diuretic or a diuretic in combination with a calcium channel blocker. However, inhibitors of the RAAS do lower blood pressure in black patients, are useful adjuncts to the recommended diuretic and calcium channel blockers, and should be used in patients with hypertension and compelling indications such as heart failure and kidney disease (especially in the presence of proteinuria) (Table 11–13). *Black patients have an elevated risk of ACE inhibitor–associated angioedema and cough, so ARBs would be the preferred choice.*

Table 11–13. Recommended antihypertensive medications.

	Antihypertensive medication					
Indication	Diuretic	Beta-blocker	ACE inhibitor	ARB	Calcium channel blocker	Aldosterone antagonist
Heart failure	√	√	√	√		√
Following MI		√	√			√
High coronary disease risk	√	√	√		√	
Diabetes	√	√	√	√	√	
Chronic kidney disease			√	√		
Recurrent stroke prevention	√		√			

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MI, myocardial infarction.

Treating Hypertension in Older Adults

Several studies in persons over 60 years of age have confirmed that antihypertensive therapy prevents fatal and nonfatal myocardial infarction and reduces overall cardiovascular mortality. The HYVET study indicated that a reasonable ultimate blood pressure goal is 150/80 mm Hg. Updated guidelines suggest that blood pressure goals should not generally be influenced by age alone. An exploratory subgroup analysis of the SPRINT study found that people older than age 75 years showed benefit at the 120 mm Hg systolic treatment target. Importantly, these

benefits were also evident in patients classified as frail. This more aggressive approach was, however, associated with greater risk of falls and worsening kidney function, indicating that close monitoring is required in elderly patients treated to lower blood pressure goals. It is also important to note the exclusion criteria of the SPRINT study, which included diabetes mellitus, stroke, and orthostatic hypotension.

Blood pressure treatment goals should be individualized in the very elderly. In the SPRINT MIND study, the lower systolic blood pressure target of 120 mm Hg was associated with a 15% reduction in the incidence of mild cognitive impairment and probable all cause dementia compared to the 140 mm Hg in the target group. Based upon this data, aggressive control of hypertension in high-risk individuals would have a significant impact on the prevalence of dementia. As discussed above, it is important to note that blood pressure measurements in the SPRINT study were made by automated devices, which are known to read lower than conventional office measurements.

How to initiate antihypertensive therapy in older patients—The same medications are used in older patients but at 50% lower doses. Pressure should be reduced more gradually with a safe intermediate systolic blood pressure goal of 160 mm Hg. As treatment is initiated, older patients should be carefully monitored for orthostasis, altered cognition, and electrolyte disturbances. The elderly are especially susceptible to problems associated with polypharmacy, including drug interactions and dosing errors.

Follow-Up of Patients Receiving Hypertension Therapy

Once blood pressure is controlled on a well-tolerated regimen, follow-up visits can be infrequent and laboratory testing limited to those appropriate for the patient and the medications used. Yearly monitoring of blood lipids is recommended, and an electrocardiogram could be repeated at 2- to 4-year intervals depending on whether initial abnormalities are present and on the presence of coronary risk factors. Patients who have had excellent blood pressure control for several years, especially if they have lost weight and initiated favorable lifestyle modifications, might be considered for a trial of reduced antihypertensive medications.

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RESISTANT HYPERTENSION

Resistant hypertension is defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic). Adherence is a major issue: the rate of partial or complete noncompliance probably approaches 50% in this group of patients; doxazosin, spironolactone, and hydrochlorothiazide were particularly unpopular in one Eastern European study based on drug assay. In the approach to resistant hypertension, the clinician should first confirm compliance and rule out "white coat hypertension," ideally using ambulatory or home-based measurement of blood pressure. Exacerbating factors should be considered (as outlined above). Finally, identifiable causes of resistant hypertension should be sought (Table 11–14). The clinician should pay particular attention to the type of diuretic being used in relation to the patient's kidney

function. Aldosterone may play an important role in resistant hypertension and aldosterone receptor blockers can be very useful. If goal blood pressure cannot be achieved following completion of these steps, consultation with a hypertension specialist should be considered. Procedure-based approaches to resistant hypertension are being developed, but the Symplicity HTN 3 study failed to show that renal sympathetic ablation improved blood pressure compared to a sham-operated control group.

Table 11–14. Causes of resistant hypertension.

Improper blood pressure measurement
Nonadherence
Volume overload and pseudotolerance
Excess sodium intake
Volume retention from kidney disease
Inadequate diuretic therapy
Drug-induced or other causes
Inadequate doses
Inappropriate combinations
Nonsteroidal anti-inflammatory drugs; cyclooxygenase-2 inhibitors
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange)
Associated conditions
Obesity
Excess alcohol intake
Identifiable causes of hypertension (see Table 11–2)

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21;289(19):2560–72.

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HYPERTENSIVE URGENCIES & EMERGENCIES

Hypertensive emergencies have become less frequent in recent years but still require prompt recognition and aggressive but careful management. A spectrum of urgent presentations exists, and the appropriate therapeutic approach varies accordingly.

Hypertensive urgencies are situations in which blood pressure must be reduced within a few hours. These include patients with asymptomatic severe hypertension (systolic blood pressure greater than 220 mm Hg or diastolic pressure greater than 125 mm Hg that persists after a period of observation) and those with optic disk edema, progressive target-organ complications, and severe perioperative hypertension. Elevated blood pressure levels alone—in the absence of symptoms of new or progressive target-organ damage—rarely require emergency therapy. Parenteral drug therapy is not usually required; partial reduction of blood pressure with relief of symptoms is the goal. Effective oral agents are clonidine, captopril, and slow-release nifedipine.

Hypertensive emergencies require substantial reduction of blood pressure within 1 hour to avoid the risk of

serious morbidity or death. Although blood pressure is usually strikingly elevated (diastolic pressure greater than 130 mm Hg), the correlation between pressure and end-organ damage is often poor. *It is the presence of critical multiple end organ injury that determines the seriousness of the emergency and the approach to treatment.* Emergencies include hypertensive encephalopathy (headache, irritability, confusion, and altered mental status due to cerebrovascular spasm), hypertensive nephropathy (hematuria, proteinuria, and acute kidney injury due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial hemorrhage, aortic dissection, preeclampsia-eclampsia, pulmonary edema, unstable angina, or myocardial infarction. Encephalopathy or nephropathy accompanying hypertensive retinopathy has historically been termed **malignant hypertension**, but the therapeutic approach is identical to that used in other hypertensive emergencies.

Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. The initial goal in hypertensive emergencies is to reduce the pressure by no more than 25% (within minutes to 1 or 2 hours) and then toward a level of 160/100 mm Hg within 2–6 hours. Excessive reductions in pressure may precipitate coronary, cerebral, or renal ischemia. To avoid such declines, the use of agents that have a predictable, dose-dependent, transient, and progressive antihypertensive effect is preferable (Table 11–15). *In that regard, the use of sublingual or oral fast-acting nifedipine preparations is best avoided.*

Table 11–15. Treatment of hypertensive emergency depending on primary site of end-organ damage. *See Table 11–16 for dosages.*

Type of Hypertensive Emergency	Recommended Drug Options and Combinations	Drugs to Avoid
Myocardial ischemia and infarction	Nicardipine plus esmolol[1] Nitroglycerin plus labetalol Nitroglycerin plus esmolol[1]	Hydralazine, diazoxide, minoxidil, nitroprusside
Acute kidney injury	Fenoldopam Nicardipine Clevidipine	
Aortic dissection	Esmolol plus nicardipine Esmolol plus clevidipine Labetalol Esmolol plus nitroprusside	Hydralazine, diazoxide, minoxidil
Acute pulmonary edema, LV systolic dysfunction	Nicardipine plus nitroglycerin[2] plus a loop diuretic Clevidipine plus nitroglycerin[2] plus a loop diuretic	Hydralazine, diazoxide, beta-blockers
Acute pulmonary edema, diastolic dysfunction	Esmolol plus low-dose nitroglycerin plus a loop diuretic Labetalol plus low-dose nitroglycerin plus a loop diuretic	
Ischemic stroke (systolic blood pressure > 180–200 mm Hg)	Nicardipine Clevidipine Labetalol	Nitroprusside, methyldopa, clonidine, nitroglycerin
Intracerebral hemorrhage (systolic blood pressure > 140–160 mm Hg)	Nicardipine Clevidipine Labetalol	Nitroprusside, methyldopa, clonidine, nitroglycerin
Hyperadrenergic states, including cocaine use	Nicardipine plus a benzodiazepine Clevidipine plus a benzodiazepine Phentolamine Labetalol	Beta-blockers
Preeclampsia, eclampsia	Labetalol Nicardipine	Diuretics, ACE inhibitors

[1]Avoid if there is LV systolic dysfunction.
[2]Drug of choice if LV systolic dysfunction is associated with ischemia.
ACE, angiotensin-converting enzyme; LV, left ventricular.

Acute ischemic stroke is often associated with marked elevation of blood pressure, which will usually fall

spontaneously. In such cases, antihypertensives should only be used if the systolic blood pressure exceeds 180–200 mm Hg, and blood pressure should be reduced cautiously by 10–15% (Table 11–15). If thrombolytics are to be given, blood pressure should be maintained at less than 185/110 mm Hg during treatment and for 24 hours following treatment.

In intracerebral hemorrhage, the aim is to minimize bleeding by reducing the systolic blood pressure in most patients to 130–140 mm Hg within the first 6 hours. In acute subarachnoid hemorrhage, as long as the bleeding source remains uncorrected, a compromise must be struck between preventing further bleeding and maintaining cerebral perfusion in the face of cerebral vasospasm. In this situation, blood pressure goals depend on the patient's usual blood pressure. In previously normotensive patients, the target should be a systolic blood pressure of 110–120 mm Hg; in hypertensive patients, blood pressure should be treated to 20% below baseline pressure. In the treatment of hypertensive emergencies complicated by (or precipitated by) central nervous system injury, labetalol or nicardipine are good choices, since they are nonsedating and do not appear to cause significant increases in cerebral blood flow or intracranial pressure. Patients with subarachnoid hemorrhage should receive nimodipine for 3 weeks following presentation to minimize cerebral vasospasm. *In hypertensive emergencies arising from catecholaminergic mechanisms, such as pheochromocytoma or cocaine use, beta-blockers can worsen the hypertension because of unopposed peripheral vasoconstriction; nicardipine, clevidipine, or phentolamine is preferred*. Labetalol is useful in these patients if the heart rate must be controlled. Table 11–15 provides guidelines for the choice of antihypertensive agent based on the site of end-organ damage. ACE inhibitors are specifically indicated for hypertensive crisis from scleroderma.

Pharmacologic Management

A. Parenteral Agents

Sodium nitroprusside is no longer the treatment of choice for acute hypertensive problems; in most situations, appropriate control of blood pressure is best achieved using combinations of nicardipine or clevidipine plus labetalol or esmolol. (Table 11–16 lists drugs, dosages, and adverse effects.)

Table 11–16. Drugs for hypertensive emergencies and urgencies (in descending order of preference).

Agent	Action	Dosage	Onset	Duration	Adverse Effects	Comments
Hypertensive Emergencies						
Nicardipine (Cardene)	Calcium channel blocker	5 mg/h intravenously; may increase by 1–2.5 mg/h every 15 minutes to 15 mg/h	1–5 minutes	3–6 hours	Hypotension, tachycardia, headache.	May precipitate myocardial ischemia.
Clevidipine (Cleviprex)	Calcium channel blocker	1–2 mg/h intravenously initially; double rate every 90 seconds until near goal, then by smaller amounts every 5–10 minutes to a maximum of 32 mg/h	2–4 minutes	5–15 minutes	Headache, nausea, vomiting.	Lipid emulsion: contraindicated in patients with allergy to soy or egg.
Labetalol (Trandate)	Beta- and alpha-blocker	20–40 mg intravenously every 10 minutes to 300 mg; 2 mg/min infusion	5–10 minutes	3–6 hours	Nausea, hypotension, bronchospasm, bradycardia, heart block.	Avoid in acute LV systolic dysfunction, asthma. May be continued orally.
Esmolol (Brevibloc)	Beta-blocker	Loading dose 500 mcg/kg intravenously over 1 minute; maintenance, 25–200 mcg/kg/min	1–2 minutes	10–30 minutes	Bradycardia, nausea.	Avoid in acute LV systolic dysfunction, asthma. Weak antihypertensive.
Fenoldopam (Corlopam)	Dopamine receptor agonist	0.1–1.6 mcg/kg/min intravenously	4–5 minutes	< 10 minutes	Reflex tachycardia, hypotension, increased intraocular pressure.	May protect kidney function.
Enalaprilat (Vasotec)	ACE inhibitor	1.25 mg intravenously every 6 hours	15 minutes	6 hours or more	Excessive hypotension.	Additive with diuretics; may be continued orally.
Furosemide (Lasix)	Diuretic	10–80 mg orally or intravenously	15 minutes	4 hours	Hypokalemia, hypotension.	Adjunct to vasodilator.
Hydralazine (Apresoline)	Vasodilator	5–20 mg intravenously; may repeat after 20 minutes	10–30 minutes	2–6 hours	Tachycardia, headache, vomiting, diarrhea	Avoid in coronary artery disease, dissection. Rarely used except in pregnancy.
Nitroglycerin	Vasodilator	0.25–5 mcg/kg/min intravenously	2–5 minutes	3–5 minutes	Headache, nausea, hypotension, bradycardia.	Tolerance may develop. Useful primarily with myocardial ischemia.
Nitroprusside (Nitropress)	Vasodilator	0.25–10 mcg/kg/min intravenously	Seconds	3–5 minutes	Anxiety, increased intracranial pressure, vomiting, bowel obstruction; thiocyanate and cyanide toxicity, especially with kidney and liver dysfunction; hypotension. Coronary steal, decreased cerebral blood flow, increased intracranial pressure.	No longer the first-line agent.
Hypertensive Urgencies						
Clonidine (Catapres)	Central sympatholytic	0.1–0.2 mg orally initially; then 0.1 mg every hour to 0.8 mg orally	30–60 minutes	6–8 hours	Sedation.	Rebound may occur.
Captopril (Capoten)	ACE inhibitor	12.5–25 mg orally	15–30 minutes	4–6 hours	Excessive hypotension.	
Nifedipine (Adalat, Procardia)	Calcium channel blocker	10 mg orally initially; may be repeated after 30 minutes	15 minutes	2–6 hours	Excessive hypotension, tachycardia, headache, angina, myocardial infarction, stroke.	Response unpredictable.

ACE, angiotensin-converting enzyme; CNS, central nervous system; GI, gastrointestinal; LV, left ventricular.

1. Nicardipine—Intravenous nicardipine is the most potent and the longest acting of the parenteral calcium channel blockers. As a primarily arterial vasodilator, it has the potential to precipitate reflex tachycardia, and for that reason it should not be used without a beta-blocker in patients with coronary artery disease.

2. Clevidipine—Intravenous clevidipine is an L-type calcium channel blocker with a 1-minute half-life, which facilitates swift and tight control of severe hypertension. It acts on arterial resistance vessels and is devoid of venodilatory or cardiodepressant effects.

3. Labetalol—This combined beta- and alpha-blocking agent is the most potent adrenergic blocker for rapid blood pressure reduction. Other beta-blockers are far less potent. Excessive blood pressure drops are unusual. Experience with this agent in hypertensive syndromes associated with pregnancy has been favorable.

4. Esmolol—This rapidly acting beta-blocker is approved only for treatment of supraventricular tachycardia, but is often used for lowering blood pressure. It is less potent than labetalol and should be reserved for patients in whom there is particular concern about serious adverse events related to beta-blockers.

5. Fenoldopam—Fenoldopam is a peripheral dopamine-1 (DA$_1$) receptor agonist that causes a dose-dependent reduction in arterial pressure without evidence of tolerance, rebound, withdrawal, or deterioration of kidney function. In higher dosage ranges, tachycardia may occur. This drug is natriuretic, which may simplify volume management in acute kidney injury.

6. Enalaprilat—This is the active form of the oral ACE inhibitor enalapril. The onset of action is usually within 15 minutes, but the peak effect may be delayed for up to 6 hours. Thus, enalaprilat is used primarily as an adjunctive agent.

7. Diuretics—Intravenous loop diuretics can be very helpful when the patient has signs of heart failure or fluid retention, but the onset of their hypotensive response is slow, making them an adjunct rather than a primary agent for hypertensive emergencies. Low dosages should be used initially (furosemide, 20 mg, or bumetanide, 0.5 mg).

They facilitate the response to vasodilators, which often stimulate fluid retention.

8. Hydralazine—Hydralazine can be given intravenously or intramuscularly, but its effect is less predictable than that of other drugs in this group. It produces reflex tachycardia and should not be given without beta-blockers in patients with possible coronary disease or aortic dissection. Hydralazine is used primarily in pregnancy and in children, but even in these situations, it is not a first-line drug.

9. Nitroglycerin, intravenous—This agent should be reserved for patients with accompanying acute coronary ischemic syndromes.

10. Nitroprusside sodium—This agent is given by controlled intravenous infusion gradually titrated to the desired effect. It lowers the blood pressure within seconds by direct arteriolar and venous dilation. Monitoring with an intra-arterial line avoids hypotension. Nitroprusside—in combination with a beta-blocker—is useful in patients with aortic dissection.

B. Oral Agents

Patients with less severe acute hypertensive syndromes can often be treated with oral therapy. Suitable drugs will reduce the blood pressure over a period of hours. In those presenting as a consequence of noncompliance, it is usually sufficient to restore the patient's previously established oral regimen.

1. Clonidine—Clonidine, 0.2 mg orally initially, followed by 0.1 mg every hour to a total of 0.8 mg, will usually lower blood pressure over a period of several hours. Sedation is frequent, and rebound hypertension may occur if the drug is stopped.

2. Captopril—Captopril, 12.5–25 mg orally, will also lower blood pressure in 15–30 minutes. The response is variable and may be excessive. Captopril is the drug of choice in the management of scleroderma hypertensive crisis.

3. Nifedipine—The effect of fast-acting nifedipine capsules is unpredictable and may be excessive, resulting in hypotension and reflex tachycardia. Because myocardial infarction and stroke have been reported in this setting, the use of sublingual nifedipine is not advised. Nifedipine retard, 20 mg orally, appears to be safe and effective.

C. Subsequent Therapy

When the blood pressure has been brought under control, combinations of oral antihypertensive agents can be added as parenteral drugs are tapered off over a period of 2–3 days.

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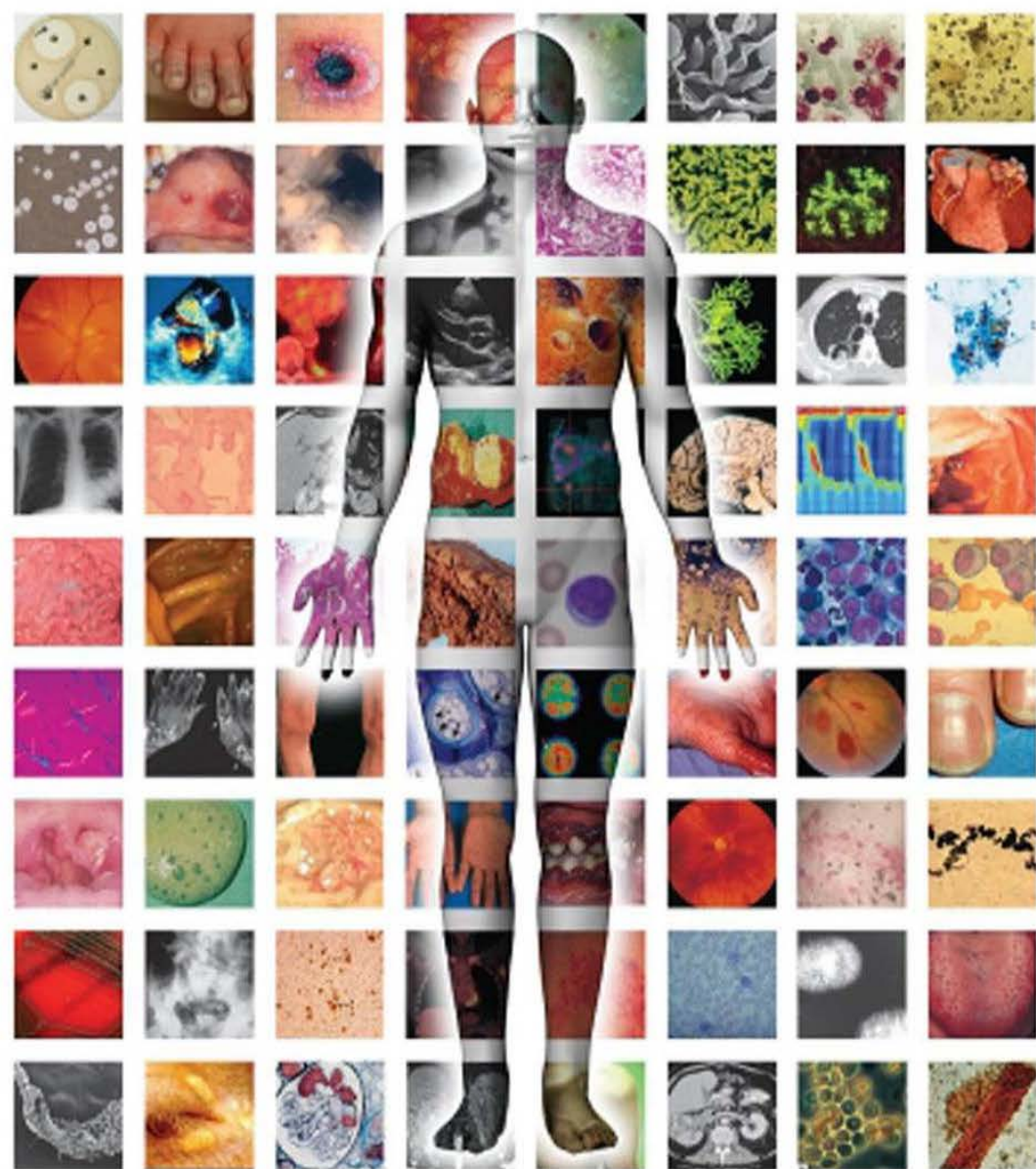Lawton MT et al. Subarachnoid hemorrhage. N Engl J Med. 2017 Jul 20;377(3):257–66. [PMID: 28723321]

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Davidson's
Principles and Practice of

23rd Edition

Medicine

<table>
<tr><td colspan="3">i   16.64   Definition of hypertension</td></tr>
</table>

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	<120	<80
Normal	<130	85
High normal	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥180	>110
Isolated systolic hypertension		
Grade 1	140–159	<90
Grade 2	≥160	<90

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i   16.65   **Causes of secondary hypertension**

Alcohol

Obesity

Pregnancy

Renal disease
- Parenchymal renal disease, particularly glomerulonephritis
- Renal vascular disease
- Polycystic kidney disease

Endocrine disease
- Phaeochromocytoma
- Cushing's syndrome
- Primary hyperaldosteronism (Conn's syndrome)
- Glucocorticoid-suppressible hyperaldosteronism
- Hyperparathyroidism
- Acromegaly
- Primary hypothyroidism
- Thyrotoxicosis
- Congenital adrenal hyperplasia due to 11β-hydroxylase or 17α-hydroxylase deficiency
- Liddle's syndrome (p. 361)
- 11β-hydroxysteroid dehydrogenase deficiency

Drugs

Coarctation of the aorta

Pathogenesis

Many factors may contribute to the regulation of BP and the development of hypertension, including renal dysfunction, peripheral resistance, vessel tone, endothelial dysfunction, autonomic tone, insulin resistance and neurohumoral factors. In more than 95% of cases, however, no specific underlying cause of hypertension can be found. Such patients are said to have essential hypertension. Hypertension is more common in some ethnic groups, particularly African Americans and Japanese, and approximately 40–60% is explained by genetic factors. Age is a strong risk factor in all ethnic groups. Important environmental factors include a high salt intake, heavy consumption of alcohol, obesity and lack of exercise. Impaired intrauterine growth and low birth weight are associated with an increased risk of hypertension later in life. In about 5% of cases, hypertension is secondary to a specific disease, as summarised in Box 16.65.

Hypertension has a number of adverse effects on the cardiovascular system. In larger arteries (>1 mm in diameter), the internal elastic lamina is thickened, smooth muscle is hypertrophied and fibrous tissue is deposited. The vessels dilate and become tortuous, and their walls become less compliant. In smaller arteries (<1 mm), hyaline arteriosclerosis occurs in the wall, the lumen narrows and aneurysms may develop. Widespread atheroma develops and may lead to coronary
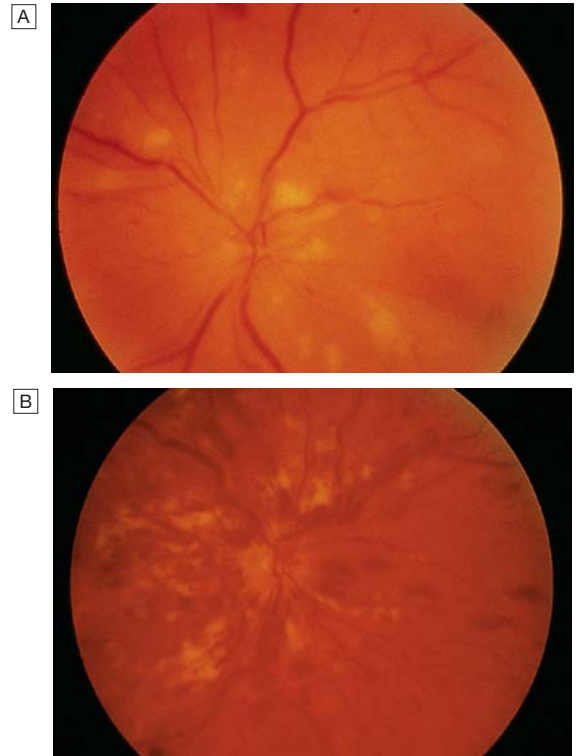
Fig. 16.76 Retinal changes in hypertension. **A** Grade 4 hypertensive retinopathy showing swollen optic disc, retinal haemorrhages and multiple cotton wool spots (infarcts). **B** Central retinal vein thrombosis showing swollen optic disc and widespread fundal haemorrhage, commonly associated with systemic hypertension. *A and B, Courtesy of Dr B. Cullen.*

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and cerebrovascular disease, particularly if other risk factors are present. These structural changes in the vasculature often perpetuate and aggravate hypertension by increasing peripheral vascular resistance and reducing renal blood flow, thereby activating the renin–angiotensin–aldosterone axis (p. 461).

Clinical features

Hypertension is usually asymptomatic until the diagnosis is made at a routine physical examination or when a complication arises. Reflecting this fact, a BP check is advisable every 5 years in adults over 40 years of age to pick up occult hypertension. Sometimes clinical features may be observed that can give a clue to the underlying cause of hypertension. These include radio-femoral delay in patients with coarctation of the aorta (see Fig. 16.93, p. 534), enlarged kidneys in patients with polycystic kidney disease (p. 405), abdominal bruits that may suggest renal artery stenosis (p. 406), and the characteristic facies and habitus of Cushing's syndrome (Box 16.65). Examination may also reveal evidence of risk factors for hypertension, such as central obesity and hyperlipidaemia. Other signs may be observed that are due to the complications of hypertension. These include signs of left ventricular hypertrophy, accentuation of the aortic component of the second heart sound, and a fourth heart sound. AF is common and may be due to diastolic dysfunction caused by left ventricular hypertrophy or the effects of CAD.

Severe hypertension can cause left ventricular failure in the absence of CAD, particularly when there is an impairment of renal function. The optic fundi are often abnormal (see Fig. 16.76 below) and there may be evidence of generalised atheroma or

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i | **16.66 Hypertensive retinopathy**

Grade 1
- Arteriolar thickening, tortuosity and increased reflectiveness ('silver wiring')

Grade 2
- Grade 1 plus constriction of veins at arterial crossings ('arteriovenous nipping')

Grade 3
- Grade 2 plus evidence of retinal ischaemia (flame-shaped or blot haemorrhages and 'cotton wool' exudates)

Grade 4
- Grade 3 plus papilloedema

16.67 How to measure blood pressure

- Use a machine that has been validated, well maintained and properly calibrated
- Measure sitting BP routinely, with additional standing BP in elderly and diabetic patients and those with possible postural hypotension; rest the patient for 2 minutes
- Remove tight clothing from the arm
- Support the arm at the level of the heart
- Use a cuff of appropriate size (the bladder must encompass more than two-thirds of the arm)
- Lower the pressure slowly (2 mmHg per second)
- Read the BP to the nearest 2 mmHg
- Use phase V (disappearance of sounds) to measure diastolic BP
- Take two measurements at each visit

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i | **16.68 Investigation of hypertension**

- Urinalysis for blood, protein and glucose
- Blood urea, electrolytes and creatinine
    Hypokalaemic alkalosis may indicate primary hyperaldosteronism but is usually due to diuretic therapy
- Blood glucose
- Serum total and HDL cholesterol
- Thyroid function tests
- 12-lead ECG (left ventricular hypertrophy, coronary artery disease)

(HDL = high-density lipoprotein)

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specific complications, such as aortic aneurysm, PAD or stroke. Examination of the optic fundi reveals a gradation of changes linked to the severity of hypertension; fundoscopy can, therefore, provide an indication of the arteriolar damage occurring elsewhere (Box 16.66). 'Cotton wool' exudates are associated with retinal ischaemia or infarction, and fade in a few weeks (Fig. 16.76A). 'Hard' exudates (small, white, dense deposits of lipid) and microaneurysms ('dot' haemorrhages) are more characteristic of diabetic retinopathy (see Fig. 27.8, p. 1176). Hypertension is also associated with central retinal vein thrombosis (Fig. 16.76B).

Investigations

A decision to embark on antihypertensive therapy effectively commits the patient to life-long treatment, so readings must be as accurate as possible. The objectives are to:
- confirm the diagnosis by obtaining accurate, representative BP measurements
- identify contributory factors and any underlying causes
- assess other risk factors and quantify cardiovascular risk
- detect any complications that are already present
- identify comorbidity that may influence the choice of antihypertensive therapy.

Blood pressure measurements

BP measurements should be made to the nearest 2 mmHg, in the sitting position with the arm supported, and repeated after 5 minutes' rest if the first recording is high (Box 16.67). To avoid spuriously high readings in obese subjects, the cuff should contain a bladder that encompasses at least two-thirds of the arm circumference. Exercise, anxiety, discomfort and unfamiliar surroundings can all lead to a transient rise in BP. Sphygmomanometry, particularly when performed by a doctor, can cause a transient elevation in BP, which has been termed 'white coat' hypertension. It has been estimated that up to 20% of patients who are found to have raised BP at outpatient clinics have a normal BP when it is recorded by automated devices used at home. The risk of cardiovascular disease in these patients is less than that in patients with sustained hypertension but greater than that in normotensive subjects. If clinic BP measurements show borderline levels of BP or if white coat hypertension is suspected, then ambulatory measurement or home-based measurements may be of value in confirming the diagnosis.

Ambulatory blood pressure measurements

A series of automated ambulatory BP measurements obtained over 24 hours or longer provide a better profile than a limited number of clinic readings and correlate more closely with evidence of target organ damage than casual BP measurements. Treatment thresholds and targets (see Box 16.71 below) must be adjusted downwards, however, because ambulatory BP readings are systematically lower (approximately 12/7 mmHg) than clinic measurements. The average ambulatory daytime (not 24-hour or night-time) BP should be used to guide management decisions.

Home blood pressure measurements

Patients can measure their own BP at home using a range of commercially available semi-automatic devices. The value of such measurements is less well established and is dependent on the environment and timing of the readings measured. Home or ambulatory BP measurements are particularly helpful in patients with unusually labile BP, those with refractory hypertension, those who may have symptomatic hypotension, and those in whom white coat hypertension is suspected.

Other investigations

All hypertensive patients should undergo a limited number of investigations (Box 16.68) but additional investigations are appropriate in patients younger than 40 years of age or those with resistant hypertension (Box 16.69). Family history, lifestyle (exercise, salt intake, smoking habit) and other risk factors should also be recorded. A careful history will identify those patients with drug- or alcohol-induced hypertension and may elicit the symptoms of other causes of secondary hypertension, such as phaeochromocytoma (paroxysmal headache, palpitation and sweating, p. 675) or complications such as CAD.

Management

The objective of antihypertensive therapy is to reduce the incidence of adverse cardiovascular events, particularly CAD, stroke and heart failure. Randomised controlled trials have

demonstrated that antihypertensive therapy can reduce the incidence of stroke and, to a lesser extent, CAD. The relative benefits (approximately 30% reduction in risk of stroke and 20% reduction in risk of CAD) are similar in all patient groups, so the absolute benefit of treatment (total number of events prevented)

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i | **16.69 Specialised investigation of hypertension**

- Chest X-ray: to detect cardiomegaly, heart failure, coarctation of the aorta
- Ambulatory BP recording: to assess borderline or 'white coat' hypertension
- Echocardiogram: to detect or quantify left ventricular hypertrophy
- Renal ultrasound: to detect possible renal disease
- Renal angiography: to detect or confirm the presence of renal artery stenosis
- Urinary catecholamines: to detect possible phaeochromocytoma (p. 675)
- Urinary cortisol and dexamethasone suppression test: to detect possible Cushing's syndrome (p. 666)
- Plasma renin activity and aldosterone: to detect possible primary aldosteronism (p. 674)

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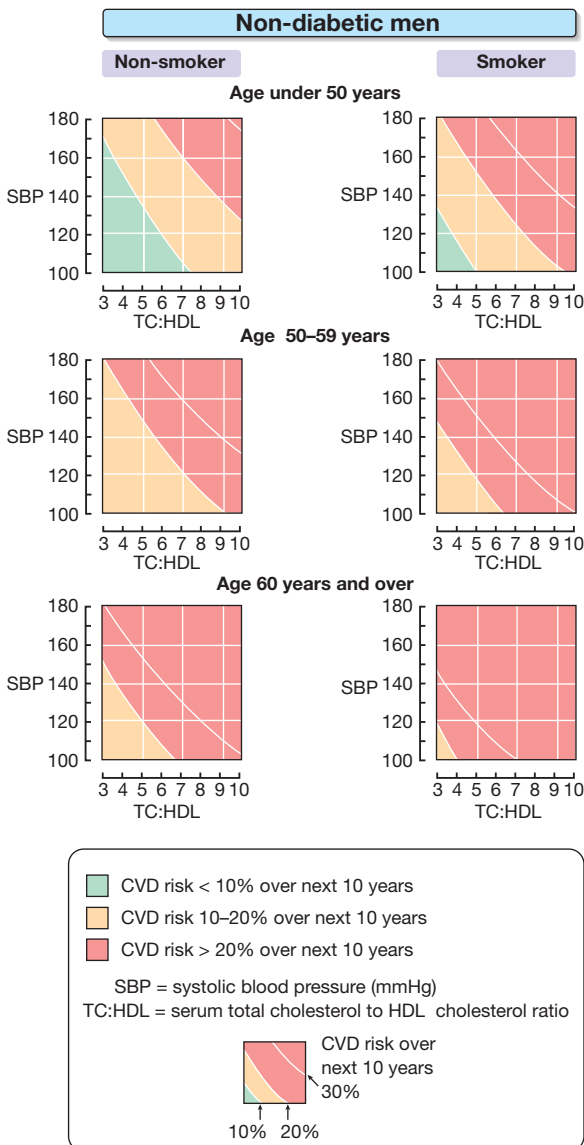
is greatest in those at highest risk. For example, to extrapolate from the Medical Research Council (MRC) Mild Hypertension Trial (1985), 566 young patients would have to be treated with bendroflumethiazide for 1 year to prevent 1 stroke, while in the MRC trial of antihypertensive treatment in the elderly (1992), 1 stroke was prevented for every 286 patients treated for 1 year.

A formal estimate of absolute cardiovascular risk, which takes account of all the relevant risk factors, may help to determine whether the likely benefits of therapy will outweigh its costs and hazards. A variety of risk algorithms are available for this purpose, such as the Joint British Societies risk calculator (Fig. 16.77 and see 'Further information'). Most of the excess morbidity and mortality associated with hypertension are attributable to CAD and many treatment guidelines are therefore based on estimates of the 10-year CAD risk. Total cardiovascular risk can be estimated by multiplying CAD risk by 4/3 (i.e. if CAD risk is 30%, cardiovascular risk is 40%). The value of this approach can be illustrated by comparing the two hypothetical cases on page 487.

Intervention thresholds

Systolic BP and diastolic BP are both powerful predictors of cardiovascular risk. The British Hypertension Society management

Fig. 16.77 Example of cardiovascular risk prediction chart for non-diabetic men. Cardiovascular risk is predicted from the patient's age, sex, smoking habit, BP and cholesterol ratio. The ratio of total to high-density lipoprotein (HDL) cholesterol can be determined in a non-fasting blood sample. Where HDL cholesterol concentration is unknown, it should be assumed to be 1 mmol/L; the lipid scale should be used as total serum cholesterol. Current guidelines suggest initiation of primary prevention in individuals with a 10-year cardiovascular risk ≥20%. Patients with diabetes mellitus should be assumed to have a 10-year cardiovascular risk of ≥20% and receive secondary prevention therapy. Modified charts exist for women. For further details, see www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information.

- To estimate an individual's absolute 10-year risk of developing cardiovascular disease (CVD), choose the panel for the appropriate gender, smoking status and age. Within this, define the level of risk from the point where the coordinates for systolic blood pressure (SBP) and ratio of the total to HDL-cholesterol cross.
- Highest-risk individuals (red areas) are those whose 10-year CVD risk exceeds 20%, which is approximately equivalent to a 10-year coronary artery disease risk of >15%. As a minimum, those with CVD risk >30% (shown by the line within the red area) should be targeted and treated now. When resources allow, others with a CVD risk >20% should be targeted progressively.
- The chart also assists in identification of individuals with a moderately high 10-year CVD risk, in the range of 10–20% (orange area) and those in whom it is <10% (green area).
- Smoking status should reflect lifetime exposure to tobacco. For further information, see www.bhf.org.uk.

From Joint British Societies Cardiovascular Risk Prediction Chart, reproduced with permission from the University of Manchester.
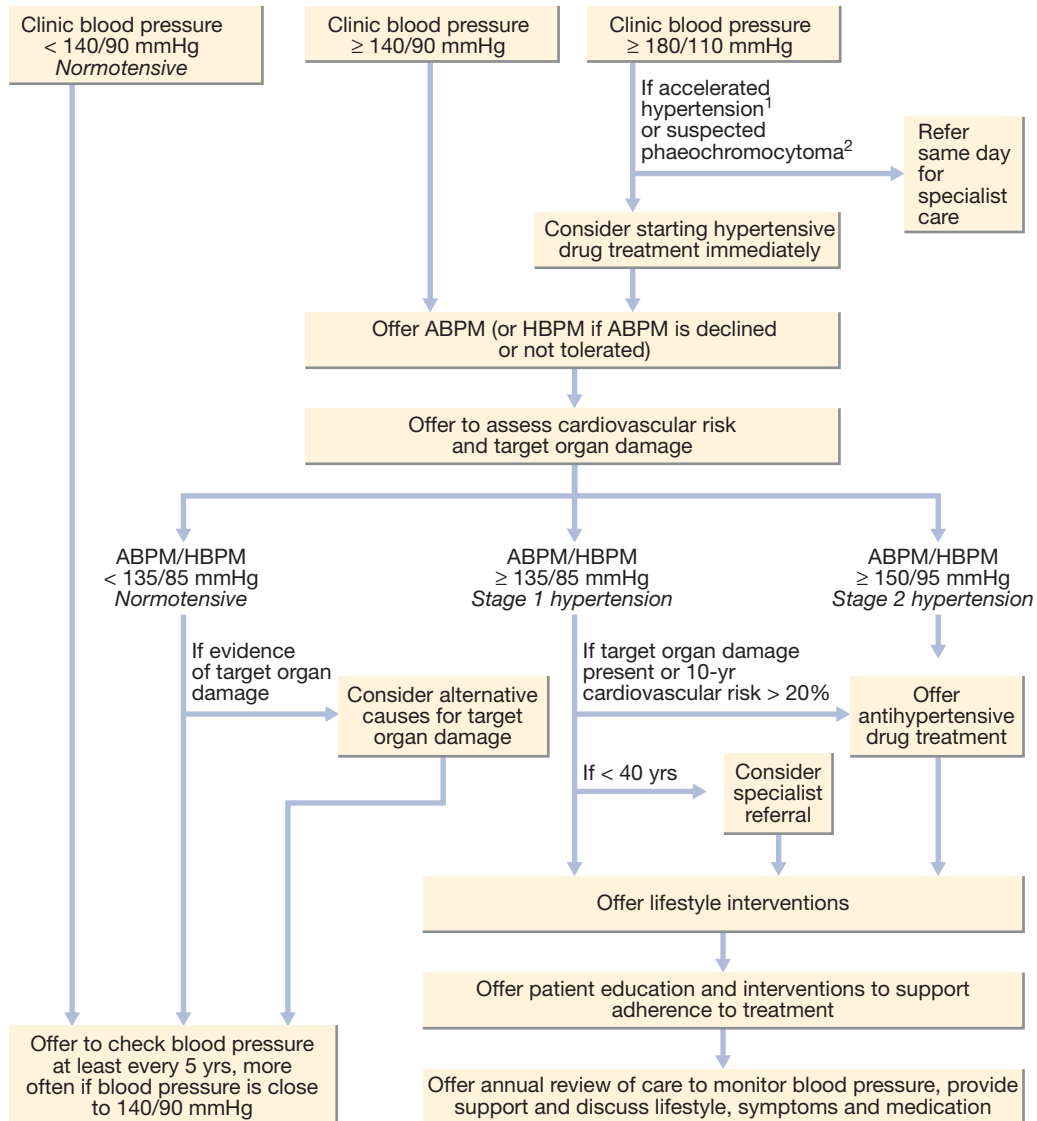
Fig. 16.78 Management of hypertension: British Hypertension Society guidelines. [1]Signs of papilloedema or retinal haemorrhage. [2]Labile or postural hypotension, headache, palpitations, pallor and diaphoresis. (ABPM = ambulatory blood pressure monitoring; HBPM = home blood pressure monitoring) *From NICE Clinical Guideline 127 – Hypertension in adults; August 2011.*

guidelines therefore utilise both readings, and treatment should be initiated if they exceed the given threshold (Fig. 16.78).

Patients with diabetes or cardiovascular disease are at particularly high risk and the threshold for initiating antihypertensive therapy is therefore lower (≥140/90 mmHg) in these patient groups. The thresholds for treatment in the elderly are the same as for younger patients (Box 16.70).

Treatment targets

The optimum BP for reduction of major cardiovascular events has been found to be 139/83 mmHg, and even lower in patients with diabetes mellitus. Moreover, reducing BP below this level causes no harm. The targets suggested by the British Hypertension Society (Box 16.71) are ambitious. Primary care strategies have been devised to improve screening and detection of hypertension that, in the past, remained undetected in up to half

16.70 Hypertension in old age

- **Prevalence**: hypertension affects more than half of all people over the age of 60 years (including isolated systolic hypertension).
- **Risks**: hypertension is the most important risk factor for myocardial infarction, heart failure and stroke in older people.
- **Benefit of treatment**: absolute benefit from therapy is greatest in older people (at least up to age 80 years).
- **Target blood pressure**: targets be relaxed in older people to 150/90 mmHg.
- **Tolerance of treatment**: antihypertensives are tolerated as well as in younger patients.
- **Drug of choice**: low-dose thiazides but, in the presence of coexistent disease such as gout or diabetes, other agents may be more appropriate.

16.71 Optimal target blood pressures[1]		
Age	Clinic BP (mmHg)	Ambulatory or home BP (mmHg)[2]
<80 years	<140/90	<135/85
≥80 years	<150/90	<140/85

[1]Both systolic and diastolic values should be attained. [2]Average BP during waking hours.

of affected individuals. Application of new guidelines should help establish patients on appropriate treatment, and allow step-up if lifestyle modification and first-line drug therapy fail to control hypertension.

Patients taking antihypertensive therapy require follow-up at regular intervals to monitor BP, minimise side-effects and reinforce lifestyle advice.

Non-drug therapy

Appropriate lifestyle measures may obviate the need for drug therapy in patients with borderline hypertension, reduce the dose and/or the number of drugs required in patients with established hypertension, and directly reduce cardiovascular risk.

Correcting obesity, reducing alcohol intake, restricting salt intake, taking regular physical exercise and increasing consumption of fruit and vegetables can all lower BP. Moreover, stopping smoking, eating oily fish and adopting a diet that is low in saturated fat may produce further reductions in cardiovascular risk that are independent of changes in BP.

Drug therapy

Thiazides The mechanism of action of these drugs is incompletely understood and it may take up to a month for the maximum effect to be observed. An appropriate daily dose is 2.5 mg bendroflumethiazide or 0.5 mg cyclopenthiazide. More potent loop diuretics, such as furosemide (40 mg daily) or bumetanide (1 mg daily), have few advantages over thiazides in the treatment of hypertension, unless there is substantial renal impairment or they are used in conjunction with an ACE inhibitor.

ACE inhibitors ACE inhibitors (enalapril 20 mg daily, ramipril 5–10 mg daily or lisinopril 10–40 mg daily) are effective and usually well tolerated. They should be used with care in patients with impaired renal function or renal artery stenosis because they can reduce glomerular filtration rate and precipitate renal failure. Electrolytes and creatinine should be checked before and 1–2 weeks after commencing therapy. Side-effects include first-dose hypotension, cough, rash, hyperkalaemia and renal dysfunction.

Angiotensin receptor blockers ARBs (irbesartan 150–300 mg daily, valsartan 40–160 mg daily) have similar efficacy to ACE inhibitors but they do not cause cough and are better tolerated.

Calcium channel antagonists Amlodipine (5–10 mg daily) and nifedipine (30–90 mg daily) are effective and usually well-tolerated antihypertensive drugs that are particularly useful in older people. Side-effects include flushing, palpitations and fluid retention. The rate-limiting calcium channel antagonists (diltiazem 200–300 mg daily, verapamil 240 mg daily) can be useful when hypertension coexists with angina but may cause bradycardia. The main side-effect of verapamil is constipation.

Beta-blockers These are no longer used as first-line antihypertensive therapy, except in patients with another indication for the drug such as angina. Metoprolol (100–200 mg daily), atenolol (50–100 mg daily) and bisoprolol (5–10 mg daily), which preferentially block cardiac β_1-adrenoceptors, should be used rather than non-selective agents that also block β_2-adrenoceptors, which mediate vasodilatation and bronchodilatation.

Combined β- and α-blockers Labetalol (200 mg–2.4 g daily in divided doses) and carvedilol (6.25–25 mg twice daily) are combined β- and α-adrenoceptor antagonists that are sometimes more effective than pure β-blockers. Labetalol can be used as an infusion in malignant phase hypertension (see below).

Other vasodilators A variety of other vasodilators may be used. These include the α_1-adrenoceptor antagonists prazosin (0.5–20 mg daily in divided doses), indoramin (25–100 mg twice daily) and doxazosin (1–16 mg daily), and drugs that act directly on vascular smooth muscle, such as hydralazine (25–100 mg twice daily) and minoxidil (10–50 mg daily). Side-effects include first-dose and postural hypotension, headache, tachycardia and fluid retention. Minoxidil also causes increased facial hair and is therefore unsuitable for female patients.

Aspirin Antiplatelet therapy is a powerful means of reducing cardiovascular risk but may cause bleeding, particularly intracerebral haemorrhage, in a small number of patients. The benefits are thought to outweigh the risks in hypertensive patients aged 50 years or over who have well-controlled BP and either target organ damage or diabetes or a 10-year CAD risk of at least 15% (or 10-year cardiovascular disease risk of at least 20%).

Statins Treating hyperlipidaemia can produce a substantial reduction in cardiovascular risk. These drugs are strongly indicated in patients who have established vascular disease, or hypertension with a high (at least 10% in 10 years) risk of developing cardiovascular disease (p. 376).

Choice of antihypertensive drug

Trials that have compared thiazides, calcium antagonists, ACE inhibitors and ARBs have not shown consistent differences in outcome, efficacy, side-effects or quality of life. Beta-blockers, which previously featured as first-line therapy in guidelines, have a weaker evidence base. The choice of antihypertensive therapy is initially dictated by the patient's age and ethnic background, although cost and convenience will influence the exact drug and preparation used. Response to initial therapy and side-effects guide subsequent treatment. Comorbid conditions also have an influence on initial drug selection (Box 16.72); for example, a β-blocker might be the most appropriate treatment for a patient with angina. Thiazide diuretics and dihydropyridine calcium channel antagonists are the most suitable drugs for treatment in older people.

Combination therapy

Although some patients can be treated with a single antihypertensive drug, a combination of drugs is often required to achieve optimal control (Fig. 16.79). Combination therapy may be desirable for other reasons; for example, low-dose therapy with two drugs may produce fewer unwanted effects than treatment with the maximum dose of a single drug. Some drug combinations have complementary or synergistic actions; for example, thiazides increase activity of the renin–angiotensin system, while ACE inhibitors block it.

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| i | 16.72 The influence of comorbidity on choice of antihypertensive drug therapy | | | |

Class of drug	Compelling indications	Possible indications	Caution	Compelling contraindications
α-blockers	Benign prostatic hypertrophy	–	Postural hypotension, heart failure[1]	Urinary incontinence
ACE inhibitors	Heart failure Left ventricular dysfunction, post-MI or established CAD Type 1 diabetic nephropathy Secondary stroke prevention[4]	Chronic renal disease[2] Type 2 diabetic nephropathy	Renal impairment[2] PAD[3]	Pregnancy Renovascular disease[2]
Angiotensin II receptor blockers	ACE inhibitor intolerance Type 2 diabetic nephropathy Hypertension with left ventricular hypertrophy Heart failure in ACE-intolerant patients, after MI	Left ventricular dysfunction after MI Intolerance of other antihypertensive drugs Proteinuric or chronic renal disease[2] Heart failure	Renal impairment[2] PAD[3]	Pregnancy
β-blockers	MI, angina Heart failure[5]	–	Heart failure[5] PAD Diabetes (except with CAD)	Asthma or chronic obstructive pulmonary disease Heart block
Calcium channel blockers (dihydropyridine)	Older patients, isolated systolic hypertension	Angina	–	–
Calcium channel blockers (rate-limiting)	Angina	Older patients	Combination with β-blockade	Atrioventricular block, heart failure
Thiazides or thiazide-like diuretics	Older patients, isolated systolic hypertension, heart failure, secondary stroke prevention	–	–	Gout[6]

[1]In heart failure when used as monotherapy. [2]ACE inhibitors or ARBs may be beneficial in chronic renal failure and renovascular disease but should be used with caution, close supervision and specialist advice when there is established and significant renal impairment. [3]Caution with ACE inhibitors and ARBs in PAD because of association with renovascular disease. [4]In combination with a thiazide or thiazide-like diuretic. [5]β-blockers are used increasingly to treat stable heart failure but may worsen acute heart failure. [6]Thiazides or thiazide-like diuretics may sometimes be necessary to control BP in people with a history of gout, ideally used in combination with allopurinol.
(ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; CAD = coronary artery disease; MI = myocardial infarction; PAD = peripheral arterial disease)

Refractory hypertension

Refractory hypertension refers to the situation where multiple drug treatments do not give adequate control of BP. Although this may be due to genuine resistance to therapy in some cases, a more common cause of treatment failure is non-adherence to drug therapy. Resistant hypertension can also be caused by failure to recognise an underlying cause, such as renal artery stenosis or phaeochromocytoma. There is no easy solution to problems with adherence but simple treatment regimens, attempts to improve rapport with the patient and careful supervision can all help. Spironolactone is a particularly useful addition in patients with treatment-resistant hypertension.

Accelerated hypertension

Accelerated or malignant hypertension is a rare condition that can complicate hypertension of any aetiology. It is characterised by accelerated microvascular damage with necrosis in the walls of small arteries and arterioles (fibrinoid necrosis) and by intravascular thrombosis. The diagnosis is based on evidence of high BP and rapidly progressive end-organ damage, such as retinopathy (grade 3 or 4), renal dysfunction (especially proteinuria) and/or hypertensive encephalopathy (see above). Left ventricular failure may occur and, if this is untreated, death occurs within months.

Management

In accelerated phase hypertension, lowering BP too quickly may compromise tissue perfusion due to altered autoregulation and can cause cerebral damage, including occipital blindness, and precipitate coronary or renal insufficiency. Even in the presence of cardiac failure or hypertensive encephalopathy, a controlled reduction to a level of about 150/90 mmHg over a period of 24–48 hours is ideal.

In most patients, it is possible to avoid parenteral therapy and bring BP under control with bed rest and oral drug therapy. Intravenous or intramuscular labetalol (2 mg/min to a maximum of 200 mg), intravenous GTN (0.6–1.2 mg/hr), intramuscular hydralazine (5 or 10 mg aliquots repeated at half-hourly intervals) and intravenous sodium nitroprusside (0.3–1.0 μg/kg body weight/min) are all effective but require careful supervision, preferably in a high-dependency unit.

Diseases of the heart valves

The heart valves allow forward movement of blood through the cardiac chambers when they are open and prevent backward flow when they are closed. Diseased valve may become narrowed, obstructing forward flow, or become leaky, causing backward flow or regurgitation. Breathlessness is a common symptom of valve disease, and acute severe breathlessness may be a presenting symptom of valve failure. The causes of this are shown in Box 16.73. Predisposition to valvular disease may be genetically determined, can arise as the result of rheumatic fever or infections, or can occur in association with dilatation of
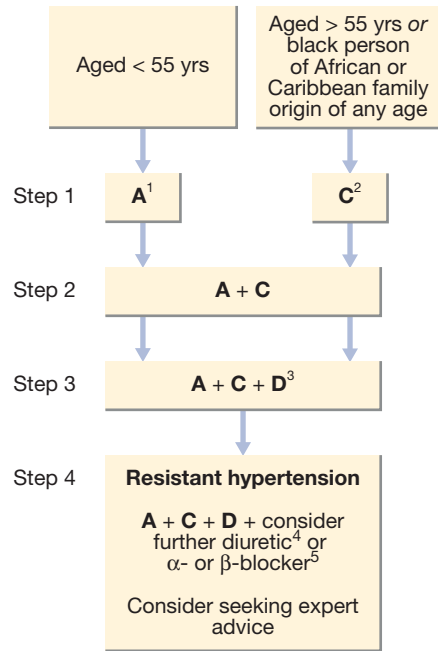
Fig. 16.79 **Antihypertensive drug combinations.** Black patients are those of African or Caribbean descent and not mixed-race, Asian or Chinese patients. [1]A = Angiotensin-converting enzyme (ACE) inhibitor or consider angiotensin II receptor blocker (ARB); choose a low-cost ARB. [2]C = calcium channel blocker (CCB); a CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure. [3]D = thiazide-type diuretic. [4]Consider a low dose of spironolactone or higher doses of a thiazide-like diuretic. At the time of publication by NICE (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. [5]Consider an α- or β-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective. *From NICE Clinical Guideline 127 – Hypertension in adults; August 2011.*

✚	16.73 **Causes of acute valve failure**

Aortic regurgitation

- Aortic dissection
- Infective endocarditis

Mitral regurgitation

- Papillary muscle rupture due to acute myocardial infarction
- Infective endocarditis
- Rupture of chordae due to myxomatous degeneration

Prosthetic valve failure

- Mechanical valves: fracture, jamming, thrombosis, dehiscence
- Biological valves: degeneration with cusp tear

the cardiac chambers in heart failure. The principal causes of valvular disease are summarised in Box 16.74.

Rheumatic heart disease

Acute rheumatic fever

Acute rheumatic fever usually affects children and young adults between the ages of 5 and 15 years. It is now rare in high-income countries in Western Europe and North America, where the

i	16.74 **Principal causes of valve disease**

Valve regurgitation

- Congenital
- Acute rheumatic carditis
- Chronic rheumatic carditis
- Infective endocarditis
- Cardiac failure*
- Syphilitic aortitis
- Traumatic valve rupture
- Senile degeneration
- Damage to chordae and papillary muscles

Valve stenosis

- Congenital
- Rheumatic carditis
- Senile degeneration

*Causes dilatation of the valve ring.

incidence is about 0.5 cases per 100 000, but remains endemic in the Indian subcontinent, Africa and South America. Recent studies indicate that the current incidence of rheumatic heart disease in India ranges between 13 and 150 cases per 100 000 population per year and it is by far the most common cause of acquired heart disease in childhood and adolescence in that country.

Pathogenesis

The condition is triggered by an immune-mediated delayed response to infection with specific strains of group A streptococci, which have antigens that cross-react with cardiac myosin and sarcolemmal membrane proteins. Antibodies produced against the streptococcal antigens cause inflammation in the endocardium, myocardium and pericardium, as well as the joints and skin. Histologically, fibrinoid degeneration is seen in the collagen of connective tissues. Aschoff nodules are pathognomonic and occur only in the heart. They are composed of multinucleated giant cells surrounded by macrophages and T lymphocytes, and are not seen until the subacute or chronic phases of rheumatic carditis.

Clinical features

Acute rheumatic fever is a multisystem disorder that usually presents with fever, anorexia, lethargy and joint pain, 2–3 weeks after an episode of streptococcal pharyngitis. There may be no history of sore throat, however. Arthritis occurs in approximately 75% of patients. Other features include rashes, subcutaneous nodules, carditis and neurological changes (Fig. 16.80). The diagnosis, made using the revised Jones criteria (Box 16.75), is based on two or more major manifestations, or one major and two or more minor manifestations, along with evidence of preceding streptococcal infection. A presumptive diagnosis of acute rheumatic fever can be made without evidence of preceding streptococcal infection in cases of isolated chorea or pancarditis, if other causes of these have been excluded. In cases of established rheumatic heart disease or prior rheumatic fever, a diagnosis of acute rheumatic fever can be made based only on the presence of multiple minor criteria and evidence of preceding group A streptococcal pharyngitis.

Carditis

Rheumatic fever causes a pancarditis involving the endocardium, myocardium and pericardium to varying degrees. Its incidence declines with increasing age, ranging from 90% at 3 years to around 30% in adolescence. It may manifest as breathlessness (due to heart failure or pericardial effusion), palpitations or chest pain (usually due to pericarditis or pancarditis). Other features include tachycardia, cardiac enlargement and new or changed
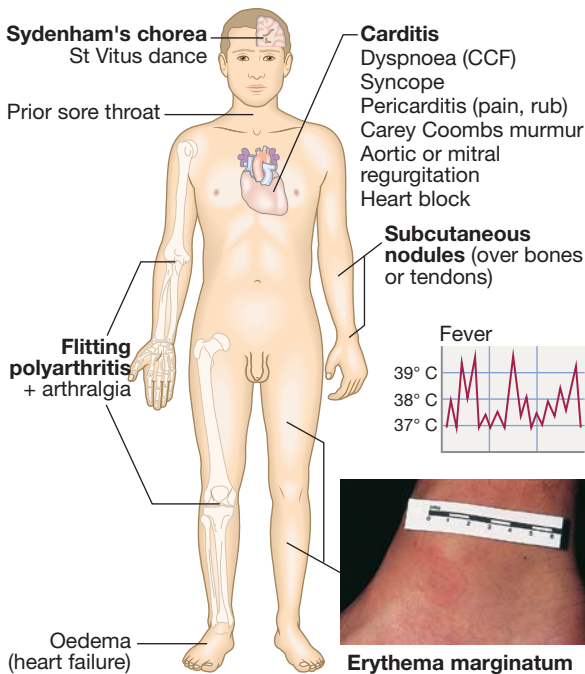
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Sydenham's chorea
St Vitus dance

Carditis
Dyspnoea (CCF)
Syncope
Pericarditis (pain, rub)
Carey Coombs murmur
Aortic or mitral regurgitation
Heart block

Prior sore throat

Subcutaneous nodules (over bones or tendons)

Fever
39° C
38° C
37° C

Flitting polyarthritis + arthralgia

Oedema (heart failure)

Erythema marginatum

Fig. 16.80 Clinical features of rheumatic fever. Bold labels indicate Jones major criteria. (CCF = congestive cardiac failure) *Inset (Erythema marginatum) From Savin JA, Hunter JAA, Hepburn NC. Skin signs in clinical medicine. London: Mosby–Wolfe, Elsevier; 1997.*

i 16.75 Jones criteria for the diagnosis of rheumatic fever

Major manifestations

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor manifestations

- Fever
- Arthralgia
- Raised erythrocyte sedimentation rate or C-reactive protein
- Previous rheumatic fever
- Leucocytosis
- First-degree atrioventricular block

Plus

- Supporting evidence of preceding streptococcal infection: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, positive throat culture*

*Evidence of recent streptococcal infection is particularly important if there is only one major manifestation.

murmurs. A soft systolic murmur due to mitral regurgitation is very common. A soft mid-diastolic murmur (the Carey Coombs murmur) is typically due to valvulitis, with nodules forming on the mitral valve leaflets. Aortic regurgitation occurs in 50% of cases but the tricuspid and pulmonary valves are rarely involved. Pericarditis may cause chest pain, a pericardial friction rub and precordial tenderness. Cardiac failure may be due to myocardial dysfunction or valvular regurgitation. ECG evidence commonly includes ST and T wave changes. Conduction defects, including AV block, sometimes occur and may cause syncope.

Arthritis

This is the most common major manifestation and occurs early when streptococcal antibody titres are high. An acute painful, asymmetric and migratory inflammation of the large joints typically affects the knees, ankles, elbows and wrists. The joints are involved in quick succession and are usually red, swollen and tender for between a day and 4 weeks.

Skin lesions

Erythema marginatum occurs in less than 5% of patients. The lesions start as red macules that fade in the centre but remain red at the edges, and occur mainly on the trunk and proximal extremities but not the face. The resulting red rings or 'margins' may coalesce or overlap (Fig. 16.80). Subcutaneous nodules occur in 5–7% of patients. They are small (0.5–2.0 cm), firm and painless, and are best felt over extensor surfaces of bone or tendons. They typically appear more than 3 weeks after the onset of other manifestations and therefore help to confirm rather than make the diagnosis.

Sydenham's chorea

Sydenham's chorea, also known as St Vitus dance, is a late neurological manifestation that appears at least 3 months after the episode of acute rheumatic fever, when all the other signs may have disappeared. It occurs in up to one-third of cases and is more common in females. Emotional lability may be the first feature and is typically followed by purposeless, involuntary, choreiform movements of the hands, feet or face. Speech may be explosive and halting. Spontaneous recovery usually occurs within a few months. Approximately one-quarter of affected patients will go on to develop chronic rheumatic valve disease.

Other features

Other systemic manifestations, such as pleurisy, pleural effusion and pneumonia, may occur but are rare.

Investigations

Blood should be taken for measurement of ESR and CRP since these are useful for monitoring progress of the disease (Box 16.76). Throat cultures should be taken but positive results are obtained in only 10–25% of cases since the infection has often resolved by the time of presentation. Serology for antistreptolysin O antibodies (ASO) should be performed. Raised levels provide supportive evidence for the diagnosis but are normal in one-fifth of adult cases of rheumatic fever and most cases of chorea. Echocardiography should be carried out and typically shows mitral regurgitation with dilatation of the mitral annulus and prolapse of the anterior mitral leaflet; it may also demonstrate aortic regurgitation and pericardial effusion.

Management

The aims of management are to limit cardiac damage and relieve symptoms.

Bed rest

Bed rest is important, as it lessens joint pain and reduces cardiac workload. The duration should be guided by symptoms, along with temperature, leucocyte count and ESR, and should be continued until these have settled. Patients can then return to normal physical activity but strenuous exercise should be avoided in those who have had carditis.

Treatment of cardiac failure

Cardiac failure should be treated as necessary. Some patients, particularly those in early adolescence, can develop a fulminant form of the disease with severe mitral regurgitation and, sometimes, concomitant aortic regurgitation. If heart failure in these cases

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119 Hypertension

■ DEFINITION
Chronic elevation in blood pressure (bp), as defined by 2017 Hypertension Guidelines (Table 119-1). Hypertension is major contributor to cardiovascular diseases and complications; etiology is unknown in 80–95% of pts ("essential hypertension"). Always consider a secondary correctable form of hypertension, especially in pts aged ≤30 or those who become hypertensive after 55. Isolated systolic hypertension (systolic ≥140, diastolic <90) most common in elderly pts, due to reduced vascular compliance.

■ SECONDARY HYPERTENSION
Renal Artery Stenosis (Renovascular Hypertension)
Due to either atherosclerosis (older men) or fibromuscular dysplasia (young women). Presents with recent onset of hypertension, refractory to usual antihypertensive therapy. Abdominal bruit is present in 50% of cases; hypokalemia due to activation of the renin-angiotensin-aldosterone system may be present.

Renal Parenchymal Disease
Elevated serum creatinine and/or abnormal urinalysis, containing protein, cells, or casts.

Coarctation of Aorta
Presents in children or young adults (including 35% of pts with Turner syndrome); constriction is usually present in aorta at origin of left subclavian artery. Examination shows diminished, delayed femoral pulsations; systolic murmur loudest at left infrascapular region. CXR shows indentation of the aorta at the level of the coarctation and rib notching (due to development of collateral arterial flow). Doppler echocardiography identifies region of constriction and measures associated pressure gradient.

Pheochromocytoma
A catecholamine-secreting tumor, typically of the adrenal medulla or extraadrenal paraganglion tissue. Presents as paroxysmal or sustained hypertension in young to middle-aged pts. Sudden episodes of headache, palpitations, and profuse diaphoresis are common. Associated findings include chronic weight loss, orthostatic *hypotension*, and impaired glucose tolerance. Pheochromocytomas may be localized to the bladder wall and may present with micturition-associated symptoms of catecholamine excess. Diagnosis is suggested by elevated plasma metanephrine level or urinary catecholamine metabolites in a 24-h urine collection (see next); the tumor is then localized by CT or MRI.

TABLE 119-1 Definition of Hypertension

CATEGORY	SYSTOLIC PRESSURE (mmHg)		DIASTOLIC PRESSURE (mmHg)
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥140	or	≥90

Source: Whelton PK, Carey RM, Aronow WS, et al: 2017 Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol* 71:e127–e248, 2018.

Hyperaldosteronism

Usually due to aldosterone-secreting adenoma or bilateral adrenal hyperplasia; a cause of refractory hypertension that should be suspected when hypokalemia is present in a hypertensive pt off diuretics (Chap. 174).

Other Causes

Oral contraceptive usage, obstructive sleep apnea (Chap. 140), Cushing's and adrenogenital syndromes (Chap. 174), thyroid disease (Chap. 173), hypercalcemia (e.g., hyperparathyroidism), and acromegaly (Chap. 171). In pts with systolic hypertension and wide pulse pressure, consider thyrotoxicosis, aortic regurgitation (Chap. 116), and systemic AV fistula.

APPROACH TO THE PATIENT

Hypertension

History: Most pts are asymptomatic. Severe hypertension may lead to headache, dizziness, or blurred vision.

Clues to specific forms of secondary hypertension: Use of medications (e.g., birth control pills, glucocorticoids, decongestants, erythropoietin, NSAIDs, cyclosporine); paroxysms of headache, sweating, or tachycardia (pheochromocytoma); history of renal disease or abdominal trauma (renal hypertension); daytime somnolence and snoring (sleep apnea).

Physical examination: Measure bp with appropriate-sized cuff (large cuff for large arm). Measure bp in both arms as well as a leg (to evaluate for aortic coarctation). Signs of hypertension include retinal arteriolar changes (narrowing/nicking); left ventricular lift, loud A_2, S_4. Clues to secondary forms of hypertension include cushingoid appearance, thyromegaly, abdominal bruit (renal artery stenosis), delayed femoral pulses (coarctation of aorta).

Laboratory Workup *Screening tests for secondary hypertension:* Should be carried out on all pts with documented hypertension: (1) serum creatinine, BUN, and urinalysis (renal parenchymal disease); (2) serum K^+ measured off diuretics (hypokalemia prompts workup for hyperaldosteronism or renal artery stenosis); (3) CXR (rib notching or indentation of distal aortic arch in coarctation of the aorta); (4) ECG (LV hypertrophy suggests chronicity of hypertension); (5) other useful screening blood tests including CBC, glucose, lipid levels, calcium, uric acid; (6) thyroid-stimulating hormone if thyroid disease suspected.

Further workup: Indicated for specific diagnoses if screening tests are abnormal or bp is refractory to antihypertensive therapy: (1) *renal artery stenosis:* captopril radionuclide scan, renal duplex ultrasound, magnetic resonance angiography, renal arteriography; (2) *Cushing's syndrome:* dexamethasone suppression test (Chap. 174); (3) *pheochromocytoma:* 24-h urine collection for catecholamines, metanephrines, and vanillylmandelic acid and/or measurement of plasma metanephrine; (4) *primary hyperaldosteronism:* depressed plasma renin activity and hypersecretion of aldosterone, both of which fail to change with volume expansion; (5) *renal parenchymal disease* (Chap. 142).

TREATMENT

Hypertension

Beneficial lifestyle modifications include weight reduction (goal BMI <25 kg/m^2); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption.

DRUG THERAPY OF ESSENTIAL HYPERTENSION (SEE TABLE 119-2)

2017 Hypertension Guidelines recommend initiating antihypertensive drug therapy for primary prevention when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (note that if 10-year atherosclerotic event risk is ≥10%, or if pt has had prior cardiovascular event, initiate drug treatment for systolic BP ≥130 or diastolic BP ≥80). Goal is to control hypertension with minimal side effects. A combination of medications with complementary actions is often required. First-line agents include diuretics, ACE inhibitors, angiotensin receptor antagonists, calcium channel antagonists, and sometimes beta blockers. On-treatment blood pressure goal is <130/80.

Diuretics

Thiazides preferred over loop diuretics because of longer duration of action; however, the latter are more potent when serum creatinine >2.5 mg/dL. Major side effects include hypokalemia, hyperglycemia, and hyperuricemia, which can be minimized by using low dosage (e.g., hydrochlorothiazide 6.25–50 mg qd). Diuretics are particularly effective in elderly and African-American pts.

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)

ACE inhibitors and ARBs are well tolerated with low frequency of side effects. May be used as monotherapy or in combination with a diuretic, calcium antagonist, or beta blocker. Side effects are uncommon and include angioedema (<1% of pts; more common with ACE inhibitors than ARBs), hyperkalemia, and azotemia (particularly in pts with elevated baseline serum creatinine). A nonproductive cough may develop in the course of therapy in up to 15% of pts on an ACE inhibitor, prompting substitution with an ARB (cough is not common side effect) or alternate antihypertensives. Note that renal function may deteriorate rapidly as a result of inhibition of the renin-angiotensin system in pts with bilateral renal artery stenosis.

Potassium supplements and potassium-sparing diuretics should be used cautiously with ACE inhibitors or ARBs to prevent hyperkalemia.

Calcium Antagonists

Direct arteriolar vasodilators; all have negative inotropic effects (particularly verapamil) and should be used cautiously if LV dysfunction is present. Verapamil and, to a lesser extent, diltiazem can result in bradycardia and AV block, so combination with beta blockers is generally avoided. Use sustained-release formulations, as short-acting dihydropyridine calcium channel blockers may increase incidence of coronary events. Common side effects include peripheral edema and constipation.

If bp proves refractory to drug therapy, evaluate for secondary forms of hypertension, especially renal artery stenosis and pheochromocytoma.

Beta Blockers

May be useful in young pts with "hyperkinetic" circulation. Begin with low dosage (e.g., metoprolol succinate 25–50 mg daily). Relative contraindications: bronchospasm, CHF, AV block, bradycardia, and "brittle" insulin-dependent diabetes.

Table 119-3 lists compelling indications for specific initial drug treatment.

SPECIAL CIRCUMSTANCES

Pregnancy

Most commonly used antihypertensives include methyldopa (250–1000 mg PO bid-tid), labetalol (100–200 mg bid), and hydralazine (10–150 mg PO bid-tid). Calcium channel blockers (e.g., nifedipine, long-acting, 30–90 mg daily) also appear to be safe in pregnancy. Beta blockers should be used cautiously; fetal hypoglycemia and low birth weights have been reported. ACE inhibitors and ARBs are *contraindicated* in pregnancy.

TABLE 119-2 Oral Drugs Commonly Used in Treatment of Hypertension

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE (DOSING FREQUENCY/DAY)	POTENTIAL ADVERSE EFFECTS
Diuretics			
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)	Hypokalemia, hyperuricemia, gout, hyperglycemia, ↑ cholesterol, ↑ triglycerides
Thiazide-like	Chlorthalidone	25–50 mg (1)	same as above
Loop diuretics	Furosemide	40–80 mg (2–3)	Hypokalemia, hyperuricemia
	Ethacrynic acid	50–100 mg (2-3)	
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	Hyperkalemia, gynecomastia
	Eplerenone	50–100 mg (1–2)	Hyperkalemia
K⁺-retaining	Amiloride	5–10 mg (1–2)	
	Triamterene	50–100 mg (1–2)	
Beta blockers			
β₁-selective	Atenolol	25–100 mg (1–2)	Bronchospasm, bradycardia, heart block, fatigue, sexual dysfunction
	Metoprolol	25–100 mg (1–2)	same as above
Nonselective	Propranolol	40–160 mg (2)	same as above
	Propranolol LA	60–180 mg (1)	same as above
Combined alpha/beta	Labetolol	200–800 mg (2)	Bronchospasm, bradycardia, heart block
	Carvedilol	12.5–50 mg (2)	

(Continued)

TABLE 119-2 Oral Drugs Commonly Used in Treatment of Hypertension (*Continued*)

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE (DOSING FREQUENCY/DAY)	POTENTIAL ADVERSE EFFECTS
ACE inhibitors	Captopril	25–200 mg (2)	Cough, hyperkalemia, azotemia, angioedema
	Lisinopril	10–40 mg (1)	
	Ramipril	2.5–20 mg (1–2)	
Angiotensin II receptor blockers	Losartan	25–100 mg (1–2)	Hyperkalemia, azotemia
	Valsartan	80–320 mg (1)	
	Candesartan	2–32 mg (1–2)	
Calcium channel antagonists			
Dihydropyridines	Nifedipine long-acting	30–60 mg (1)	Edema, constipation
Nondihydropyridines	Verapamil long-acting	120–360 mg (1–2)	Edema, constipation, bradycardia, heart block
	Diltiazem long-acting	180–420 mg (1)	

TABLE 119-3 Guidelines for Selecting Initial Drug Treatment of Hypertension

CLASS OF DRUG	COMPELLING INDICATIONS	POSSIBLE INDICATIONS	COMPELLING CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS
Diuretics	Heart failure Elderly pts Systolic hypertension		Gout	
Beta blockers	Angina	Heart failure	Uncontrolled asthma and COPD	Athletes and physically active pts
	After MI	Pregnancy	Heart block[a]	
	Tachyarrhythmias			Peripheral vascular disease
ACE inhibitors	Heart failure	Chronic renal parenchymal disease	Pregnancy	
	LV dysfunction		Hyperkalemia	
	Following an MI		Bilateral renal artery stenosis	
	Diabetic nephropathy			
Angiotensin receptor blockers	ACE inhibitor cough	Chronic renal parenchymal disease	Pregnancy	
	Heart failure		Bilateral renal artery stenosis	
	Diabetic nephropathy		Hyperkalemia	
Calcium channel blockers	Angina Elderly pts Systolic hypertension	Peripheral vascular disease	Heart block[b]	Heart failure with reduced ejection fraction[c]

[a]Second- or third-degree atrioventricular block.
[b]Second- or third-degree atrioventricular block with verapamil or diltiazem.
[c]Verapamil or diltiazem.
Abbreviations: ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease.

TABLE 119-4 Usual Intravenous Doses of Antihypertensive Agents Used in Hypertensive Emergencies[a]

ANTIHYPERTENSIVE AGENT	IV DOSE
Nitroprusside	Initial 0.3 (mcg/kg)/min; usual 2–4 (mcg/kg)/min; maximum 10 (mcg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg or 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 mcg/kg over 1 min, then 50–300 (mcg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 mcg/min, then titrate by 5 mcg/min at 3–5 min intervals; if no response is seen at 20 mcg/min, incremental increases of 10–20 mcg/min may be used
Hydralazine	10–50 mg at 30-min intervals

[a]Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

Renal Disease

Standard thiazide diuretics may not be effective. Consider metolazone, furosemide, or bumetanide, alone or in combination.

Diabetes

Consider ACE inhibitors and angiotensin receptor blockers as first-line therapy to control bp and slow renal function deterioration.

Malignant Hypertension

Defined as an abrupt increase in bp in pt with chronic hypertension or sudden onset of severe hypertension; a medical emergency. Immediate therapy is mandatory if there is evidence of cardiac decompensation (CHF, angina), encephalopathy (headache, seizures, visual disturbances), or deteriorating renal function. Inquire about use of cocaine, amphetamines, or monoamine oxidase inhibitors. Drugs to treat hypertensive crisis are listed in Table 119-4. In absence of hypertensive encephalopathy, goal is to lower mean arterial pressure gradually over several hours to prevent precipitous reduction in cerebral, coronary, and renal blood flow. Replace with PO antihypertensive as pt becomes asymptomatic and bp improves.

KUMAR & CLARK'S

Clinical Medicine

Tenth Edition

Adam Feather
David Randall
Mona Waterhouse

ELSEVIER

31

Hypertension

Vikas Kapil

CORE SKILLS AND KNOWLEDGE

Hypertension is a major cardiovascular risk factor affecting one-third of the adult population. It should be managed as part of a comprehensive cardiovascular risk reduction strategy, while also assessing for hypertensive end-organ damage and ruling out secondary causes. Treatment involves modifying lifestyle to improve diet and body weight, and making use of a range of antihypertensive medications.

Most hypertension is managed in primary care. However, young patients with hypertension, or patients who have uncontrolled hypertension despite taking three or more antihypertensives, should be referred for expert evaluation. Doctors may subspecialize in the management of hypertension after completing training in clinical pharmacology, cardiology, renal medicine or another medical specialty.

Key skills in hypertension include:
- diagnosing appropriately, and placing this in the context of an individual's overall cardiovascular risk
- screening for secondary causes of hypertension and seeking evidence of end-organ damage
- understanding the evidence-based guidelines for treating hypertension, and becoming familiar with the main classes of drug used.

Gaining experience in the practical management of hypertension is best done during primary care attachments: for instance, by observing patients undergoing annual blood pressure medication reviews with their general practitioner. Attending a specialist hypertension clinic in a secondary or tertiary care setting gives an interesting insight into secondary causes and more severe phenotypes of hypertension.

INTRODUCTION

Raised blood pressure (BP) is the leading risk factor for death worldwide, outstripping tobacco smoking, poor sanitation and infectious diseases. It is a leading risk factor for atrial fibrillation, stroke, myocardial infarction and end-stage kidney disease. It is such a powerful predictor of these cardiovascular events that modern drug therapies are licensed for cardiovascular protection simply on evidence of sustained BP reduction.

Hypertension refers to the *persistent elevation of BP in the systemic arterial circulation*. It is the most common chronic health condition for which patients receive medication from their primary care doctor and is associated with 1 in 10 of all primary care appointments. It affects one-third of adults and this number continues to rise in all populations. Annual drug costs related to hypertension are well in excess of £1 billion in the UK.

Hypertension is diagnosed against threshold levels of BP from the evidence gathered from large multicentre, multinational studies.

However, given the continuous relationship between BP and cardiovascular disease (Fig. 31.1) and renal morbidity, there is a trend towards basing treatment on even lower thresholds, and towards using total *cardiovascular risk* (see p. 751) to guide decisions on whether lowering BP is of benefit in individual patients. The majority of patients with hypertension are managed in primary care, with specialist hospital services usually reserved for evaluation of secondary causes, or for those patients with problematic BP phenotypes (see p. 1136) or medication intolerances.

Despite the wide availability of diagnostics (i.e. BP monitors) and proven treatments (i.e. medications), reduction of BP in hypertensive patients to target levels is less than 50% in most populations and remains the focus of renewed efforts on an international, national and local scale.

Hypertension is a disease of *ageing*. It is rare in children and adolescents, and a diagnosis in those under 30 years of age requires careful evaluation of possible underlying secondary causes (see p. 1136). Due to age-related stiffening in large arterial structure
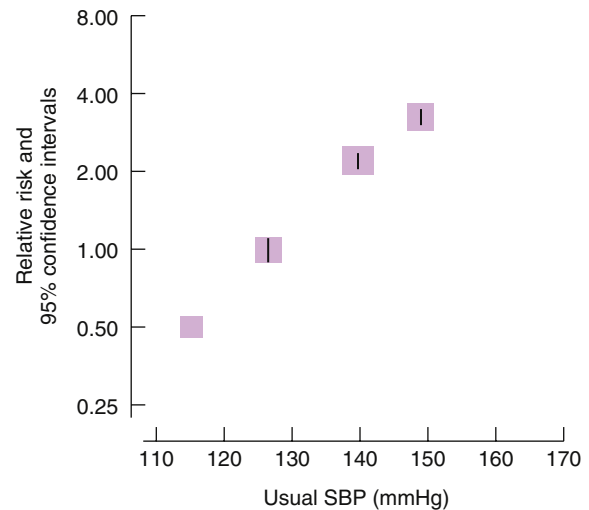
SBP and CHD
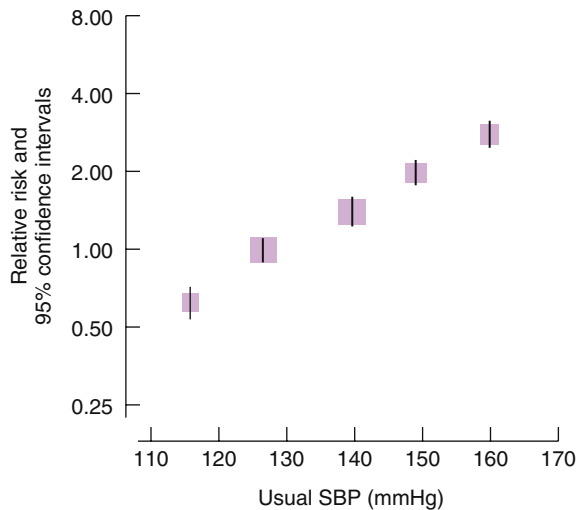
SBP and stroke

Fig. 31.1 The relationship between blood pressure and cardiovascular morbidity. CHD, coronary heart disease; SBP, systolic blood pressure. (Jackson et al. Lancet 2005; 365: 434-441.)

(arteriosclerosis), BP tends to increase throughout middle and later life. Female sex hormones appear to protect against raised BP, as women have lower BP levels at all ages until menopause, when both prevalence of hypertension and achieved BP levels approximate to those of men. Hypertension is more common in certain ethnic groups (black African, African–Caribbean) and is also associated with urbanized and migrant populations, although an unequivocal explanation for these phenomena is not agreed.

CLINICAL APPROACH TO THE PATIENT WITH HYPERTENSION

Hypertension is largely asymptomatic, though it is associated with increased prevalence of headaches, epistaxis and, less commonly, other neurological symptoms such as visual disturbance and dizziness. Furthermore, in the absence of a hypertensive emergency syndrome (see p. 1144), symptoms related to raised BP are not an indication for treatment. Indeed, antihypertensive therapy is more likely to be the cause of adverse symptoms, such as postural intolerance. History and examination should seek out identifiable causes of raised BP and asymptomatic organ damage.

There are four key considerations in the clinical assessment of patients with hypertension (**Fig. 31.2**) that can be determined through history, examination and investigations:
- What is the true BP level?
- Is there an identifiable reason for high BP?
- Does the BP level require lowering?
- Are there compelling reasons to use certain therapeutic approaches above others?

History

This should cover:
- symptoms of hypertension or secondary causes
- lifestyle issues: weight, alcohol excess, stimulant recreational drug use, tobacco smoking, exercise, stressors (work and personal)
- family history
- pregnancy
- adherence to antihypertensives.

Examination and investigations

These should include:
- 'out-of-office' BP level
- asymptomatic organ damage: eyes, kidneys, heart (**Fig. 31.2**)
- exclusion of secondary causes where relevant
- estimation of total cardiovascular risk.

MEASUREMENT OF BLOOD PRESSURE

Due to the non-continuous, pulsatile blood flow maintained by the cardiac cycle, BP is represented by two numbers: systolic (peak arterial pressure during cardiac contraction) and diastolic (lowest arterial pressure during cardiac relaxation). It is presented as *systolic pressure/diastolic pressure in mmHg* (millimetres of mercury). BP is dynamic and has patterns of variability over seconds (related to breathing, sympathetic activation), minutes (exertion), hours (wake–sleep, circadian hormonal patterns) and the longer term (seasonal). Therefore, the measurement of BP and its use to determine the treatment of hypertension are inherently imprecise and a single measure may not reliably represent the usual (real) BP and its contribution to overall cardiovascular risk. As with any biological variable, the true usual BP is better approximated with multiple measurements at each assessment, and sometimes over several different assessment episodes, before decisions are made regarding changes in treatment.

BP can be measured in several different locations on the body, though readings are traditionally taken in the non-dominant arm. Initially, the BP may be checked in both arms; if there is a significant difference (usually considered to be >10 mmHg), then the arm with the higher BP is used for subsequent measurements.

It is important to measure BP in the correct manner. Methodological variation can falsely and hugely over- or underestimate BP.

History
- duration of hypertension
- symptoms (headaches, vision, epistaxis – usually asymptomatic)
- co-morbidities (diabetes, CKD, CAD, stroke, gout)
- family history, particularly young hypertension and cardio-renal events
- hypertensive disorders of pregnancy, active attempt to become pregnant
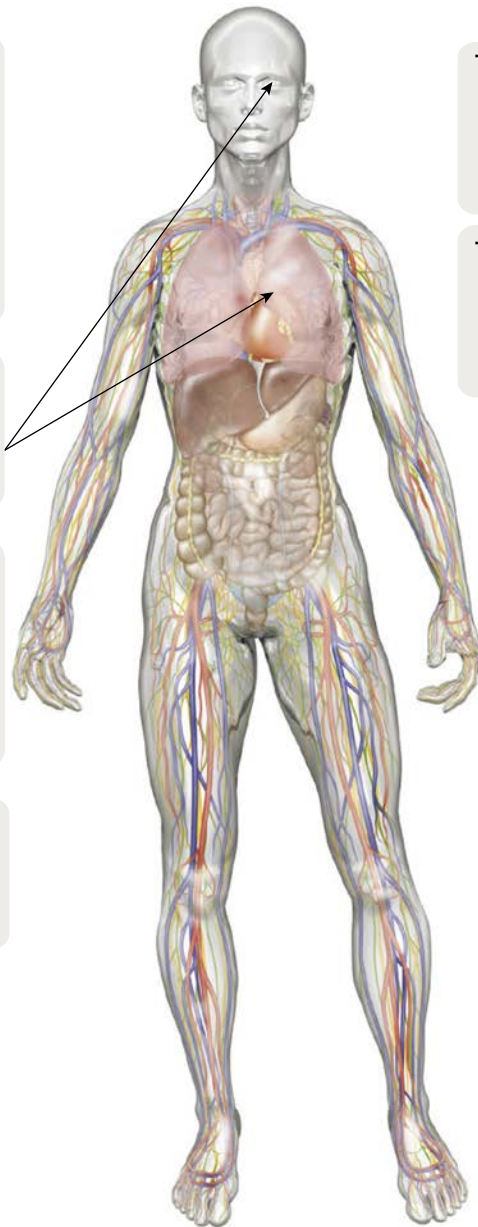- Secondary causes - see Box 31.2

Examination
- Target organ disease:
  - fundoscopy
  - cardiac palpation and auscultation
- Secondary causes - see Box 31.2

Investigations
- Target organ disease
  - urine reagent strip testing and ACR
  - eGFR
  - ECG
- CV risk   - lipids
          - Hba$_{1c}$
- Secondary causes - see Box 31.2

Measurement
- Office   - correct technique
          - >1 reading
- Out-of-office   - ambulatory
          - home

Thresholds (mmHg)
Under 80 years: >140 or >90 (office) or >135 or >85 (ambulatory or home)
Over 80 years: >160 or >90 (office) or >150 or >85 (ambulatory or home)

Target (mmHg)
- In UK, <140/90 if <80 years and <150/90 if >80 years)
- Growing international trend to aim for <130/80 in all patients if tolerated

Aims of the examination:
- Seeking signs of end organ damage and dysfunction including retinal disease, heart failure, stroke and chronic kidney disease
- Assessing associated cardiovascular risk factors - blood glucose, stigmata of hyperlipidaemia
- In the younger adult - looking for rarer secondary causes e.g. Cushingoid features, acromegaly, renal masses.

Fig. 31.2 Clinical assessment in hypertension. ACR, albumin : creatinine ratio; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

For static measurements (office/surgery, home), BP should be measured in the seated position after 5 minutes' uninterrupted rest, with the back supported and the legs uncrossed. The BP bladder should encircle at least 80% of the upper arm circumference and should be placed at the level of the heart; the arm should be supported (**Fig. 31.3**).

Although the unit of BP is still 'millimetres of mercury' (mmHg), mercuric sphygmomanometers are obsolete. Modern monitors are usually electronic, oscillometric devices that are automated and have been validated against mercuric devices or intra-arterial BP catheters.

One situation where auscultatory (i.e. using a cuff and stethoscope to listen over the brachial artery) methods are still preferred is in **atrial fibrillation** (see p. 1059), where variations in pulse volume and rapid variation in BP due to variable left ventricular filling time lead to inaccuracies when oscillometric BP machines are used, especially when ventricular rates are uncontrolled. In particular, diastolic BP tends to be poorly estimated in this situation.

Office/surgery measurement

This refers to measurement of the BP by a healthcare professional in a healthcare setting, such as a primary care surgery or hospital outpatient department. This is the most established method of measurement and all clinical trials of antihypertensive drugs have used it to assess for inclusion and for titration towards target.

It is established practice to take more than two sequential BP readings and to use either the mean or the lowest of these to represent office BP.
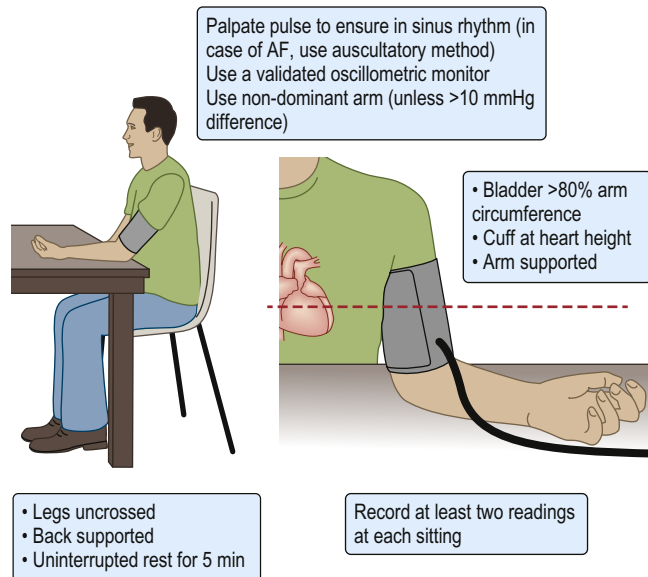
Palpate pulse to ensure in sinus rhythm (in case of AF, use auscultatory method)
Use a validated oscillometric monitor
Use non-dominant arm (unless >10 mmHg difference)

• Bladder >80% arm circumference
• Cuff at heart height
• Arm supported

• Legs uncrossed
• Back supported
• Uninterrupted rest for 5 min

Record at least two readings at each sitting

Fig. 31.3 The correct way to measure blood pressure. AF, atrial fibrillation.

Issues with this approach include:
- a requirement for healthcare professionals and setting (expense, time)
- a requirement for multiple visits to obtain sufficient data for decision-making (expense, time)
- a 'white coat effect': for most people, BP measured by healthcare professionals is approximately 5/5 mmHg higher than at home, though there is inter-individual variation in the magnitude
- the fact that home and ambulatory BP measurements are more predictive of cardiovascular events, as patients do not live in healthcare settings.

Although office BP is no longer recommended as the sole measure for diagnosis in many guidelines, it is still advocated for on-going monitoring and medication titration, as no cardiovascular outcome trials have used out-of-office readings to adjust treatment.

Home measurement

This is measurement of BP at home by the patients themselves, using the same type of machine as in the clinic. It is a type of 'out-of-office' BP measurement and is closely approximated to daytime ambulatory BP. It is particularly useful for:
- identification of different BP phenotypes
- engagement of patients in healthcare and shared decision-making
- long-term monitoring of BP between healthcare visits.

Current recommendations suggest that BP is measured on two or more occasions in sequence, in the morning prior to medicines and again in the evening for 4–7 days. The initial day's readings are discarded and the rest of the values are averaged to calculate home BP. This BP is highly predictive of cardiovascular events and tends to be approximately 5/5 mmHg lower than that measured in the clinic.

Issues with this approach include:
- a requirement for patients to obtain their own machine (expense)
- a requirement for training
- the lack of objective readings (i.e. the measurements are often patient-reported averages, rather than independent evaluations).

? Box 31.1 Phenotypes of hypertension and corresponding BP measurements

Phenotype/method	Office BP	Out-of-office BP	Cardiovascular risk
Normotension	Normal	Normal	Lowest
White coat hypertension	High	Normal	Intermediate
Masked hypertension	Normal	High	Intermediate
Hypertension	High	High	Highest

Ambulatory measurement

Ambulatory BP monitors are portable, oscillometric devices that measure BP discontinuously throughout a 24-hour period, most commonly every 20–30 minutes during waking hours and every 30–60 minutes during sleep.

The large number of readings that this provides gives an accurate estimate of true BP. The 24-hour mean of the sequence of daytime and nocturnal BP measurements is more predictive of cardiovascular events than both home and office BP measurements. Ambulatory BP monitoring is now recommended in the UK instead of office BP for diagnosis, and is recommended as a complementary strategy to office BP in most other high-income health economies.

Similar to home BP, ambulatory BP allows in a single measurement:
- improved diagnostic accuracy over office BP
- identification of different BP phenotypes.

Daytime ambulatory BP is 5–10/5 mmHg lower than office BP in the same patient. Issues with this approach include dislike of repeated BP measurement, especially at night.

PHENOTYPES OF HYPERTENSION

The measurement techniques described can describe different phenotypes of hypertension (**Box 31.1**). Although both **white coat hypertension** and **masked hypertension** represent intermediate cardiovascular risk phenotypes, masked hypertension is treated using out-of-office values to guide treatment, while antihypertensives are not recommended for use in white coat hypertension, despite elevated cardiovascular risk, due to a current lack of evidence.

There are other common phenotypes of hypertension:

Isolated systolic hypertension

Due to age-related arterial stiffening, systolic BP continues to rise in patients above 50 years of age, with a corresponding reduction in diastolic BP. This widening **pulse pressure** (the difference between systolic and diastolic BP, usually <50 mmHg) is associated with increased vascular damage. Drug treatment in isolated systolic hypertension is the same as for combined hypertension (where both systolic and diastolic BP are elevated), though care is needed not to reduce diastolic BP below 60 mmHg, which could cause problems with coronary blood flow (largely due to diastolic flow/pressure). Aortic valve incompetence can also cause an isolated systolic phenotype, though this is normally apparent on cardiac auscultation and/or echocardiography.
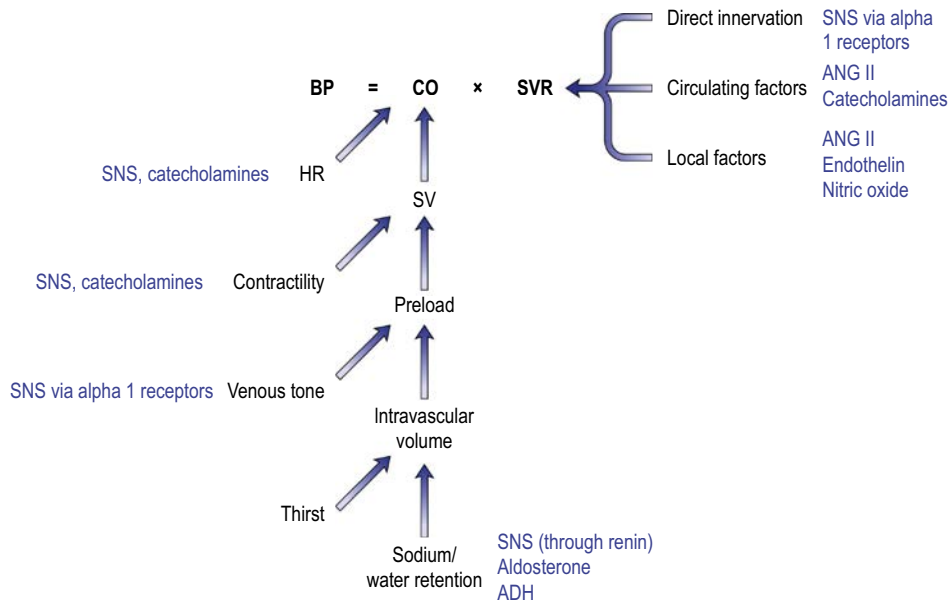
Fig. 31.4 The main mechanisms affecting BP. ANGII, angiotensin II; CO, cardiac output; HR, heart rate; SNS, sympathetic nervous system; SVR, systemic vascular resistance.

Orthostatic hypotension

This refers to a sustained fall in BP within 3 minutes of assuming an upright position of either more than 20 mmHg systolic or more than 10 mmHg diastolic BP. It is more common in older age, and in conditions associated with *autonomic neuropathies,* such as diabetes mellitus and Parkinson's disease. It is typically asymptomatic, although it can cause postural intolerance or instability, *dizziness* and falls. It should be actively screened for in those with typical symptoms or risk factors. Most guidelines recommend using the standing BP as the true BP value for guiding treatment.

Variable blood pressure

Although BP is a highly dynamic variable, the degree of variability is exaggerated in some patients. This is often due to disorders of the autonomic nervous or endocrine system. Reliable assessment is achieved only through a combination of repeated short-term (ambulatory) and long-term (home) methodologies. Management of BP levels in such patients is often complex and best performed in specialist clinics.

CAUSES OF RAISED BLOOD PRESSURE

Up to 90% of patients have no singular identifiable cause of their elevated BP; this is called *primary hypertension* (preferred to the historical term, 'essential hypertension', see later). Advances in genomic research have increased our understanding of polygenic effects on BP (see p. 30). We now know that several hundred genes are individually associated with prevalent BP levels but that each one contributes only small amounts (perhaps 0.5–1 mmHg). Combined, however, they may account for 60% of the BP level in any one person. As such, a family history of hypertension is common, though a family history of hypertension or strokes at unusually young ages should instigate careful evaluation for secondary causes. While there are a large number of distinct genetic influences on BP regulation, for the purposes of clinical assessment and management the main mechanisms affecting BP are *vascular volume*

and tone, and *cardiac output* (Fig. 31.4). The remaining effects on BP (up to 40%) are mediated by environmental (e.g. temperature, noise) and lifestyle stressors (e.g. diet).

Sudden development of severe hypertension or worsening of previously good control should alert healthcare professionals to the need for careful evaluation of adherence, and for consideration of lifestyle and secondary causes of hypertension if adherence is confirmed. Adherence issues and causes of secondary hypertension should also be borne in mind in patients with *resistant hypertension* (usually defined as uncontrolled BP despite three separate, guideline-recommended antihypertensives).

Lifestyle-related issues

Diet

Relevant *dietary* information provided by patients is often inaccurate. Nevertheless, some clear dietary patterns are associated with raised BP:
- high salt intake
- low vegetable and fruit intake
- high saturated fat intake
- high simple carbohydrate intake
- excessive liquorice (inhibits an enzyme that normally prevents cortisol from activating the mineralocorticoid receptor).

Lack of exercise

Both cardiovascular and strength training forms of *exercise* are associated with lower BP values, along with other health benefits.

Population interventions

In view of the potential effects of these lifestyle issues, together with those associated with obesity (see later), population approaches are increasingly being taken to reduce BP, including:
- public health education drives to:
  - reduce salt and body weight
  - increase exercise

- regulatory approaches to reducing salt in processed foods
- consideration of sugar taxes and minimum alcohol unit pricing.

Drugs

Many patients with hypertension will have other co-morbidities that require additional pharmacological treatment, and consideration should therefore be given to the possible interference of these other drugs with BP control. Both over-the-counter medicines, such as non-steroidal anti-inflammatory drugs (NSAIDs), and recreational drugs, such as alcohol and sympathomimetic stimulants, should be taken into account, as patients may not mention them when a history is being taken unless specific enquiry is made.

Commonly implicated drugs that raise BP include:

- alcohol
- stimulant, recreational drugs
- oral contraceptive pill
- NSAIDs
- corticosteroids
- calcineurin inhibitors
- vascular endothelial growth factor inhibitors
- some antidepressants (e.g. venlafaxine).

Secondary hypertension

Hypertension can have an identifiable singular cause, removal or reversal of which leads to normalization of BP. These are *secondary causes* of hypertension, and are broadly categorised into renal, vascular, endocrine and neural problems (**Box 31.2**). Together, these are present in only 10% of all hypertensive patients (though this proportion is higher in those under 30 years of age). The most common causes of secondary hypertension are largely thought to be *primary hyperaldosteronism* (increased salt/water retention), *obstructive sleep apnoea* and *obesity* (the last two causing sympathetic overdrive), though the precise proportions ascribed to these and other causes vary in different studies due to advances in evaluation and diagnostics.

Although it is not usually considered a secondary cause, *pregnancy* can be associated with raised BP. The normal physiological response to pregnancy is an increase in circulating volume that is offset by significant vasodilation, leading to lower BP, particularly in the second trimester. However, in some pregnant women, defects in placental formation or vascularity lead to pregnancy-induced hypertension and/or *pre-eclampsia* (see p. 1454). Hypertension associated with pregnancy often improves within a few months of the infant's delivery but women with hypertensive disorders of pregnancy are more likely to develop hypertension earlier in life than age-matched controls. The history should establish whether women of childbearing age are actively trying to become pregnant, as many of the first-line drugs are not recommended in this situation (see **Box 31.6**).

THRESHOLDS AND TARGETS IN HYPERTENSION

Primary hypertension used to be termed 'essential' as, in the 19th century, raised BP was largely thought to be an appropriate physiological adaptation. However, with the advent of randomized clinical trials and modern therapeutics, evidence has grown that lowering BP is beneficial, reducing both cardiorenal events and overall mortality.

The first Veterans Administration Cooperation study randomized patients with a diastolic BP of 115–129 mmHg to active or placebo

treatments. By modern standards, this would be considered to be severe hypertension, yet we know of the benefit of lowering BP only from these and subsequent trials.

Since around 1990, the threshold for diagnosis of hypertension has mostly been an office BP of more than 140 mmHg systolic or more than 90 mmHg diastolic (whichever is *worse*). Treatment has largely been reserved for those with *grade 2 hypertension* (**Box 31.3**), as there is a large evidence base for lowering BP with medications in these patients. For *grade 1 hypertension*, it has been usual practice to persevere with lifestyle changes to lower BP and to recommend immediate treatment for those with an overall elevated cardiovascular risk (>1% per year, using validated cardiovascular risk equations), or evidence of organ injury due to hypertension (hypertensive target organ damage). Drug therapy is advocated, however, if BP fails to normalize after a 3–12-month period of best-tolerated lifestyle changes.

For the most part, then, the target has been an office BP of less than 140/90 mmHg, with stricter targets for patients with diabetes and proteinuric chronic renal disease (<130/80 mmHg). However, recent trials such as SPRINT and meta-analysis of other trials have suggested that there is incremental benefit in targeting all patients to a BP below 130/80 mmHg; this is reflected in most international guidelines, though not currently in those produced by the National Institute for Health and Care Excellence (NICE) in the UK.

In older people (over 80 years), there is less evidence for treating mild hypertension, and most guidelines recommend treating only moderate (i.e. grade 2) hypertension. Some guidelines (e.g. NICE) suggest a lax target office BP of below 150/90 mmHg in patients diagnosed over 80 years of age. However, age is often used incorrectly as a surrogate for frailty, and although there is good reason to lower BP cautiously and judiciously in the frail elderly or in those at increased risk of falls or postural hypotension, there is a similar trend in some up-to-date international guidelines, such as those of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH), to reduce office BP to below 130/80 mm Hg in biologically fit elderly patients, if tolerated.

There are additional considerations relating to these values. As mentioned, there has been a consistent shift to using out-of-office methods, preferably ambulatory, for diagnosis. Because these methods avoid any white coat effect, the thresholds for diagnosis are based on different numerical values, usually considered to be 5–10/5 mmHg lower than in the office.

Further reading

The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373:2103–2116.
Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39:3021–3104.

HYPERTENSIVE TARGET ORGAN DAMAGE

Hypertension can cause structural or functional changes in the heart, kidney and central nervous system that may be regarded as intermediate end-points with respect to reducing absolute clinical end-points of myocardial infarction, heart failure, end-stage renal disease and strokes.

Eyes

Direct ophthalmoscopy (fundoscopy) of the dilated eye is recommended in most guidelines for evaluation of hypertensive vascular changes. The most commonly used grading classification is the

Box 31.2 Drivers/secondary causes of hypertension

System	Causes	History	Examination	Investigations	Management
Lifestyle	Diet	Dietary history		24 h urinary sodium excretion (as a guide and to track improvement in salt intake)	Dietary advice
	Lack of exercise	<30 min/day moderate-intensity exercise			Exercise advice
Drugs	Alcohol	Alcohol history, features of alcohol dependence	May have signs of chronic liver disease	Only if indicated for underlying liver disease	Alcohol reduction <14 units/week
	BP-increasing medications	Medication history, including supplements, recreational and over-the-counter		Use of reference sources to identify BP-increasing medications	Cessation, switching where possible
	Poor adherence to antihypertensives	Validated adherence questionnaires Open, non-judgemental attitude		Urine or plasma qualitative drug monitoring	Shared decision-making, single-pill combinations
Metabolic	Obesity	Recent weight gain	Body mass index >30		Weight loss advice, bariatric surgery
Vascular	Coarctation of aorta		Unequal arm–arm or arm–leg pulses or BP Cardiac murmur or abdominal bruit	MR or CT angiography of whole aorta	Surgery, angioplasty of conservative
Renal	Renal artery stenosis	Sudden deterioration in renal function with ACE inhibitor/ARB Flash pulmonary oedema with normal cardiac function	Abdominal bruit	MR or CT renal angiogram	Balloon angioplasty ± stenting
	Chronic kidney disease	Childhood UTIs Features of vasculitis/GN (see p. 1360)	Ballotable renal masses (PKD) Vasculitic rash	Urine dipstick and ACR eGFR Renal ultrasound Immunological tests (if GN likely) Renal biopsy (if GN likely)	Treatment of BP Treatment of underlying inflammatory renal disease
Endocrine	Primary hyperaldosteronism	Weakness, fatigue		Low K, raised aldosterone:renin MRI/CT adrenal ± adrenal vein sampling	Laparoscopic adrenalectomy if unilateral secretion
	Hypercortisolaemia	Weight gain, fatigue	Centripetal weight distribution, hirsutism, pigmented striae	Low-dose dexamethasone suppression (cortisol should normally be low)	Laparoscopic adrenalectomy or pituitary surgery, depending on source
	Phaeochromocytoma	Palpitations, sweating, BP surges, dizziness, pallor, anxiety	Associated with neurofibromatosis-1	Plasma metanephrines MIBG scan/MRI chest/abdomen/pelvis to localize	Surgery after sufficient alpha blockade
	Acromegaly	Sweating, skin tags, growth of soft tissues, visual disturbance	Large hands, feet, interdental separation, bitemporal hemianopia	Serum IGF-1	Pituitary surgery
	Thyroid (both hypo- and hyperthyroidism)	Weight gain, tiredness (hypothyroidism) Irritability, weight loss (hyperthyroidism)	Pretibial myxoedema, slow relaxing reflex (hypothyroidism) exophthalmos, acropachy (hyperthyroidism)	Serum TSH	Thyroxine replacement (hypothyroidism) or thyroid blockade/surgery (hyperthyroidism)
Respiratory	Obstructive sleep apnoea (p. 960)	Daytime somnolence (Epworth score), snoring, nocturnal sweating, morning headaches	Large neck, Mallampati score 3 or 4	Overnight oximetry (screening) Sleep study	Weight loss Mandibular advancement device CPAP
Neurological	Autonomic failure	Postural intolerance, thermoregulatory issues, parkinsonism	Variable BP Supine hypertension with normal or low BP sitting, standing	24 h BP: nocturnal hypertension Autonomic function testing	Symptom-based, nocturnal medication if supine hypertension
Obstetric	Pregnancy	Secondary amenorrhoea Visual disturbance, oedema, headaches, seizures (for PET/eclampsia only)	Fundal palpation	Urine or serum β-hCG	Pregnancy-safe medicines Delivery of fetus

ACE, angiotensin-converting enzyme; ACR, albumin:creatinine ratio; ARB, angiotensin II receptor blocker; CPAP, continuous positive airways pressure; CT, computed tomography; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; hCG, human chorionic gonadotrophin; IGF-1, insulin-like growth factor 1; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; PKD, polycystic kidney disease; TSH, thyroid stimulating hormone; UTI, urinary tract infection.

Description	Office BP (mmHg)		Daytime ambulatory or home BP (mmHg)	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
Normal BP	<130	<80	n/a	n/a
High-normal BP	130–139	80–89	n/a	n/a
Grade 1 hypertension	140–159	90–99	135–149	85–94
Grade 2 hypertension	160–179	100–109	150–169	95–104
Severe hypertension	>180	>110	>170	>105
Isolated systolic hypertension	>140	<90	>135	<85

Keith–Wagener–Barker system, comprising four distinct ophthalmic hypertensive phenotypes (*retinopathy*). More recent evaluation, however, has suggested combining the two milder phenotypes, leaving three grades to consider (**Fig. 31.5**):

- *Mild:* Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking (modest association with cardiovascular and cerebral events).
- *Moderate:* Haemorrhage (blot, dot or flame-shaped), micro-aneurysm, cotton-wool spot, hard exudate, or a combination of these signs (strong association with cardiovascular and cerebral events).
- *Severe:* Signs of moderate retinopathy plus papilloedema (swelling of optic head) (strong association with cardiovascular events, stroke and death).

Heart

The heart is a muscle and hypertrophy may occur in response to increased workload. Left ventricular remodelling is initially a compensatory phenomenon to reduce wall stress but eventually leads to a pathogenic increase in left ventricular mass.

Hypertensive left ventricular hypertrophy is usually asymptomatic but can be detected as a thrusting apex beat on precordial palpation. It is also sometimes detected on standard 12-lead electrocardiography (ECG), demonstrating various patterns of increased voltages in the chest leads and T-wave abnormalities (see **Fig. 30.79**). There are many different scoring systems for ECG criteria for diagnosing left ventricular hypertrophy; all are quite insensitive (20–50%) but specificity is better (>90%), which means that if criteria are positive, true left ventricular hypertrophy is likely to be present.

ECGs are recommended in all hypertensive patients, as they are widely available and cheap, and do not require much in the way of additional training to interpret, especially as modern ECG machines have in-built reporting algorithms. However, cardiac imaging, using transthoracic echocardiography and cardiac MRI, is more sensitive and specific than ECG (when compared to autopsy data), though access, cost and need for additional trained staff to conduct and report these tests limit their wide utility and acceptance in all hypertensive patients. These cardiac imaging modalities can estimate the actual mass of the left ventricle; this is indexed to height and weight, and has sex-specific normal values.

Kidney

Kidney disease is both a cause and a consequence of hypertension. Early hypertensive kidney damage is most easily detectable through an increase in microalbuminuria on urine test strips or as an increased laboratory albumin : creatinine ratio. Estimates of glomerular filtration rate (GFR), based on serum creatinine and demographic criteria, are also obtained, especially as several antihypertensive medications are potentially nephrotoxic. However, there is usually an initial reduction in GFR associated with chronic BP-lowering from any cause, and this usually reflects intra-renal haemodynamic changes rather than intrinsic renal damage; it is therefore common practice to allow GFR to reduce by up to 10% on initiation of antihypertensive therapy. More regular follow-up is mandated to ensure that this does not indicate progressive renal decline.

TREATMENT

Meta-analyses of large-scale RCTs have shown that a 10/5 mmHg reduction in BP is associated with a 15% reduction in all-cause mortality, 35% reduction in stroke, 40% reduction in heart failure and 20% reduction in myocardial infarction. Hypertension is treated to reduce these major cardiovascular and renal events. For this reason, treatment of hypertension without managing other modifiable cardiovascular risk factors (raised cholesterol, diabetes mellitus, tobacco smoking, obesity) is suboptimal. Cardiovascular risk scores, such as QRISK2®, are useful for integrating all of these risk factors, to judge when there is benefit in treating hypertensive patients. Ten-year risk estimates are less useful than lifetime risk estimates in young patients, given the powerful role of age in all cardiovascular risk scores.

Lifestyle changes

These are recommended for all hypertensive patients, irrespective of grade or duration of disease. The BP reductions accompanying such lifestyle changes are complementary and similar in magnitude (compared to half-standard monotherapy) to those achieved by antihypertensive medications (**Box 31.4**).

Bariatric surgery is indicated for those with hypertension and a body mass index (BMI) of more than 35 kg/m^2, but it is not commonly performed without the additional co-morbidity of type 2 diabetes. Recent data confirm the profound BP-lowering effect of such surgery, which may be due to additional gut hormonal changes postoperatively, in addition to expected weight loss.

Drug treatment

A single antihypertensive medication at standard dose reduces BP by about 9/5 mmHg in mild hypertension. Although patients with mild hypertension may achieve control with monotherapy, those with moderate or worse hypertension invariably require several drugs in combination. Greater effects are obtained by combining medications from different classes, targeting different mechanisms. Three antihypertensives at half-standard dose reduce BP by 20/11 mmHg. Most *adverse effects* with antihypertensives, in keeping with most pharmaceuticals, are type A adverse reactions (see p. 258) and are thus dose-dependent. Keeping doses to a minimum but combining different classes minimizes the chances of adverse effects and maximizes the likelihood of effectively lowering BP to target levels.

As mentioned, *adherence* is increasingly recognized as a key barrier to achieving BP control. Although there are different validated measures to assess this, such as the Morisky-8 Medication
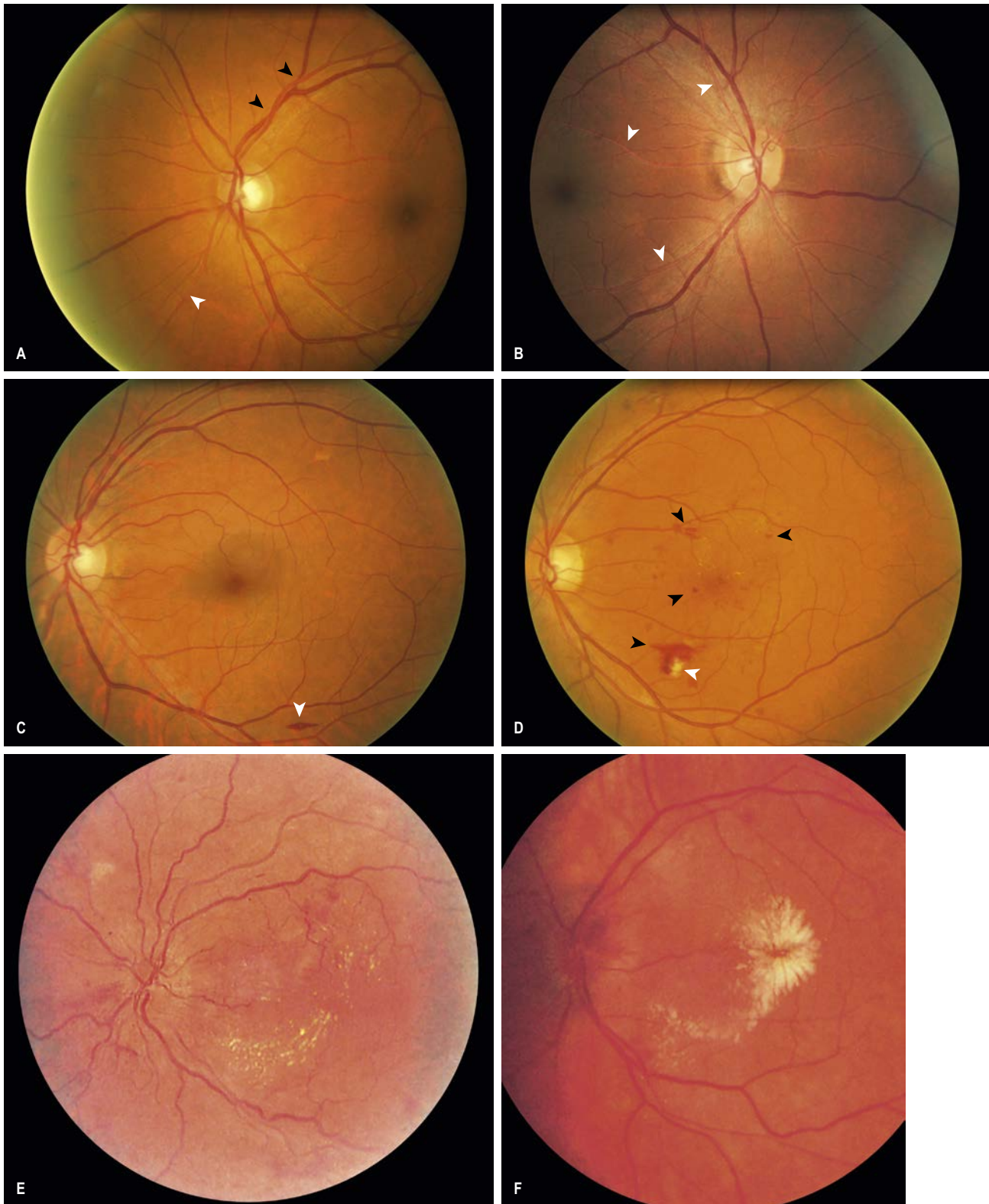
Fig. 31.5 Hypertensive retinopathy. (A–B) Examples of *mild hypertensive retinopathy*. **(A)** Arteriovenous nicking (black arrows) and focal narrowing (white arrow). **(B)** Opacification (silver or copper wiring) of arteriolar wall (white arrows). **(C–D)** Examples of *moderate hypertensive retinopathy*. **(C)** A flame-shaped retinal haemorrhage (white arrow). **(D)** A cotton-wool spot (white arrow), retinal haemor-rhages and microaneurysms (black arrows). **(E–F)** *Severe hypertensive retinopathy*. **(E)** Exudates and flame haemorrhages in grade 3 retinopathy. **(F)** Signs of malignant hypertension in grade 4 disease, with a swollen optic disc and macular exudate. (*A–D From Schachat AP, Sadda SVR, Hinton DR et al.* Ryan's Retina, *6th edn. Elsevier Inc., 2018, Figs 52.1 and 52.2; E–F from Innes JA, Dover AR, Fairhurst K.* Macleod's Clinical Examination, *14th edn. Elsevier Ltd, 2018, Fig. 8.18CD.*)

_i_   Box 31.4 Impact of lifestyle changes on BP

Lifestyle change	Expected mean BP reduction
Regular cardiovascular exercise (30 min daily)	5 mmHg
Weight reduction if overweight (body mass index >25 kg/m²)	1 mmHg/kg
Increased intake of fruits and vegetables, reduced intake of saturated fat	10 mmHg
Dietary salt reduction <6 g day	5 mmHg
Alcohol <2 units daily	3 mmHg

Adherence Scale (**Box 31.5**), along with prescription refill rate (whether patients receive a resupply at the right time to have therapy every day), modern drug analytical techniques on plasma or urine have demonstrated that question-/refill-based assessment correlates poorly to objective evidence of measurable drug in biological matrices. From these newer techniques, it appears that up to two-thirds of patients in specialist care do not take some or any of their antihypertensive medications. There are no easy solutions to such covert non-adherence but keeping an open, non-judgemental approach can facilitate the volunteering of this information and then shared-decision making can determine how best to proceed and what patients want for their own health.

In view of this, and with evidence that suggests there is an elevated cardiovascular risk when control is achieved over protracted (>6 months) timeframes, guidelines have recently tended to abandon monotherapy and suggest starting with a combination of medicines to achieve BP control effectively and rapidly. Current ESH/ESC guidelines have taken this further and have used evidence that single-pill combinations of two or more antihypertensive medications improve adherence to suggest that most patients should be started on single-pill combination therapy.

There are numerous classes of antihypertensive medication available and their key features are described in **Box 31.6**.

Most guidelines recommend choosing one (or two) of the following three classes of drugs, as initial therapy:
- angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBS),
- calcium channel blockers
- thiazide-like diuretics.

Current UK NICE guidelines use age and ethnicity as surrogates for plasma renin activity. Older and black African ancestries are associated with low renin status and so have reduced responsiveness to drugs ACEIs and ARBs as monotherapy: hence calcium-channel blockers are recommended in these groups. Younger white patients are recommended to start on an ACEI or ARB. These are largely thought to be interchangeable, except that ARBs are better tolerated, with less cough and angio-oedema.

There is clear evidence from the PATHWAY-2 study that spironolactone is the best fourth-line drug, in preference to beta- or alpha-blockers, though it is unlicensed for this indication in most countries and patients should be appropriately counselled. Once a patient is on three or four drugs and remains uncontrolled (**_resistant hypertension_**), they should be referred for specialist assessment.

In keeping with the view that reduction in total cardiovascular risk is paramount, cholesterol-lowering therapy, most commonly with small doses of potent statins, is recommended in all patients with a total cardiovascular risk of more than 1% per year. This

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_i_   Box 31.5 Morisky Medication Adherence Scale[a]

Please answer each question, based on your personal experience with your medications. Note that there is no right or wrong answer.

1. Do you sometimes forget to take your medications?	No	Yes
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medications?	No	Yes
3. Have you ever cut back or stopped taking your medications without telling your doctor because you felt worse when you took it?	No	Yes
4. When you travel or leave home, do you sometimes forget to bring along your medications?	No	Yes
5. Did you take your medications yesterday?	No	Yes
6. When you feel that your health condition is under control, do you sometimes stop taking your medications?	No	Yes
7. Taking medications every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	No	Yes
8. How often do you have difficulty remembering to take all your medications?	Never/rarely Once in a while Sometimes Usually All the time	1 0 0 0 0

'No' answers to questions 1–4, 6 and 7, a 'Yes' answer to question 5 and 'Never/rarely' to question 8 score 1. A score of 8 suggests good adherence. Score of 7 or less suggests poor adherence and is associated with poorer BP control. (_Adapted from Morisky DE, Ang A, Krousel-Wood M et al. Predictive validity of a medication adherence measure in an outpatient setting._ J Clin Hypertens _2008; 10:348–354.)_

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threshold may not be reached in younger patients due to the power of age in the risk calculators, and so a more long-term view of risk reduction should be taken in these patients. Although low-dose aspirin has been used in **_primary cardiovascular prevention_** for many decades, contemporary large-scale trials have not demonstrated a net benefit on mortality, even in patients with diabetes, with any gains from reduction in cardiovascular events offset by increases in bleeding events. Given these data, aspirin is no longer recommended in any patient group for primary prevention.

Further reading

Ettehad D, Emdin CA, Kiran A et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. _Lancet_ 2016; 387:957–967.

Morisky DE, Ang A, Krousel-Wood M et al. Predictive validity of a medication adherence measure in an outpatient setting. _J Clin Hypertens_ 2008; 10:348–354.

Williams B, MacDonald TM, Morant M et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. _Lancet_ 2015; 386:2059–2068.

https://www.qrisk.org/three/. _Cardiovascular risk score calculator_.

Future approaches

Poor hypertension control rates are apparent with available prescribed medicines, largely due to adherence issues rather than

? Box 31.6 Main classes of antihypertensive agent and their key features

Class	Mechanism	Adverse effects	Compelling indication	Compelling contra-indication	Monitoring	Example
Angiotensin-converting enzyme (ACE) inhibitor	Reduce angiotensin II vasoconstriction	Cough Angio-oedema Hyperkalaemia		Bilateral RAS Angio-oedema	eGFR, K	Ramipril 2.5–10 mg daily
Angiotensin II receptor blockers (ARB)	Reduce angiotensin II vasoconstriction	Hyperkalaemia		Bilateral RAS	eGFR, K	Losartan 25–100 mg daily
Dihydropyridine calcium-channel blocker (DHP CCB)	Peripheral vasodilation	Constipation, headache, oedema	Nifedipine/amlodipine recommended for use in pregnancy			Amlodipine 5–10 mg daily
Non-DHP CCB	Peripheral vasodilation	Constipation, bradycardia		High grade atrioventricular block Bradycardia	Heart rate	Verapamil 120–480 mg daily
Thiazide-like diuretic	Vasodilation, salt/water loss	Hyponatraemia, hypokalaemia, hyperuricaemia, hyperglycaemia	Heart failure	Gout	Serum electrolytes, HbA$_{1c}$, urate	Indapamide 1.5–2.5 mg daily
Potassium-sparing diuretic	Salt/water loss	Hyponatraemia, hyperkalaemia, gynaecomastia	Primary hyperaldosteronism Resistant hypertension	eGFR <30 mL/min K >5.0 mmol/L	Serum electrolytes	Spironolactone 25–50 mg daily
Beta-blocker	Vasodilation through renin inhibition, sympatholysis	Bradycardia, sleep disturbance, bronchospasm	Heart failure with reduced ejection fraction Ischaemic heart disease Labetalol licensed in pregnancy	Asthma High-grade atrioventricular block Bradycardia	Heart rate	Bisoprolol 2.5–10 mg daily
Alpha-blocker	Venodilation	Postural hypotension, urine incontinence, oedema	Suspected phaeochromocytoma Benign prostatic hypertrophy	Urinary incontinence Postural hypotension Heart failure		Doxazosin 1–8 mg twice daily
Central	Sympatholysis	Depression, drowsiness, dry mouth	Methyldopa licensed in pregnancy	Mood disorders Heart failure with reduced ejection fraction	Rebound hypertension on cessation	Methyldopa 250–500 mg 3 times daily

eGFR, estimated glomerular filtration rate; K, potassium; RAS, renin–angiotensin system.

ineffectiveness of the drugs. Nevertheless, patients are keen to explore medicine-free mechanisms to lower BP.

Neural sympathetic signalling has a key role in vascular homeostasis, with effects mediated via afferent renal and aortic/carotid baroreceptor functions. Novel interventional approaches to alter this signalling are currently under evaluation to improve BP in both medicine-naive and treated hypertensive patients. The most advanced, in terms of regulatory pathways and evidence base, is renal sympathetic denervation. This group of procedures uses modern endovascular catheter-based approaches to the renal sympathetic nerves, which lie on the outside of the renal artery. Catheters can then deliver energy (radio-frequency, ultrasound) or neurotoxins (such as alcohol) across the renal artery wall to reach the sympathetic nerves and abrogate afferent signalling to the vasomotor centres, thus reducing total sympathetic drive and BP. Although the technological advancements are impressive and there is evidence of robust BP-lowering using modern out-of-office measurements, the magnitude of these effects is similar to that of antihypertensive monotherapy and thus most patients will still require drug therapy to control BP in the long term. Furthermore, these are new technologies: the long-term safety of the procedures is not clear, as regards

the renal artery or otherwise, and there are no outcome studies investigating cardiac, renal, stroke or death end-points using any technology apart from drugs.

Further reading

Schlaich MP. Renal sympathetic denervation: a viable option for treating resistant hypertension. *Am J Hypertens* 2017; 30:847–856.
Townsend RR, Mahfoud F, Kandzari DE et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017; 390:2160–2170.

MANAGING BLOOD PRESSURE IN HOSPITAL

Perioperative period

Preoperative

Uncontrolled hypertension is a common reason for cancellation of elective surgical procedures. Patients with severely elevated BP (>180/110 mmHg) are associated with greater perioperative harm, such as myocardial injury, though there is no clear evidence that

reducing BP acutely in the preoperative period to controlled levels is beneficial. Patients with uncontrolled BP (evidence of chronic poor control of >160/100 mmHg in treated patients, or opportunistic measurements in pre-assessment in previously normotensive patients of >180/110 mmHg) are commonly referred back to their primary care doctor for adequate management of hypertension prior to elective procedures, though this is not a reason to delay necessary emergency surgical intervention. Although ACEIs and ARBs are often withheld arbitrarily for 24 hours preoperatively, it is usual to continue antihypertensive medications throughout the perioperative period unless there is documented hypotension or other related issues, such as withholding nephrotoxic antihypertensives if there is acute kidney injury.

Intraoperative

Sympathetic activation during induction of anaesthesia can cause elevation of BP by 30 mmHg, with far larger responses in patients with untreated hypertension. Subsequently, with maintenance of anaesthesia, BP tends to fall due to the direct sympatholytic and vasodilating actions of anaesthetic drugs and loss of baroreflex regulation of BP. Patients with pre-existing uncontrolled hypertension are more likely to experience intraoperative BP lability (i.e. hypotension or hypertension), which is a risk factor for myocardial ischaemia and injury. Intraoperative hypertension is most commonly associated with inadequate analgesia or depth of anaesthesia, though it is prudent and recommended to exclude serious problems with airway, oxygen delivery and breathing first.

Postoperative

Pain and (inadvertent) omission of antihypertensive medications are the most common reasons for postoperative hypertension. Once these factors have been corrected, there are no data to support the further active lowering of BP in the postoperative period without evidence of acute end-organ damage, though it is usual practice to try to keep BP below 180/110 mmHg, in part to reduce the risk of problems with postoperative haemostasis.

Blood pressure on the wards

Patients with hypertension are often admitted to hospital for other medical reasons. Various factors can contribute to acute elevations of BP, such as antihypertensive medication omission, drug-induced hypertension (see earlier), anxiety, pain, bladder distension, recreational drug withdrawal and neurological injury. In the absence of a hypertensive emergency or other co-morbidity that requires acute BP management (e.g. to facilitate thrombolysis in acute stroke), uncontrolled BP does not require immediate management.

However, as with most phenotypes, there is a threshold value that makes most healthcare professionals anxious about increased cerebral and cardiovascular risk, even in inpatients, and it is therefore common for BPs consistently above 180/110 mmHg to be treated, where there is no other clear precipitant. There is no role for short-acting drugs, such as sublingual glyceryl trinitrate (GTN) or nifedipine, and titration of standard chronic therapies with on-going monitoring is preferred.

Hypertensive emergencies

Only a small subset of patients with significantly elevated BP (usually >180/120 mmHg) have signs or symptoms of acute target-organ damage, termed hypertensive emergencies. The rate and magnitude of any increase in BP may be more important than the absolute level of BP in determining the severity of organ injury; this is key in obstetric medicine, where the usual BP in younger women may be verging on hypotensive (90–110/60–70 mmHg), and pre-eclampsia may develop with a BP over 140/90 mmHg.

In all hypertensive emergencies, intravenous antihypertensive medication therapy is indicated to cause rapid reduction of BP, as this is thought to minimize on-going organ damage and prevent or reduce the risk of morbidity and mortality. The timing, magnitude and other considerations related to the management of these conditions are considered in **Box 31.7**.

Referral to specialist care

The majority of hypertensive patients are managed in primary care. Apart from the clear indications related to hypertensive emergencies described earlier, there are other reasons to mandate referral to specialist secondary care:

- Patients taking ≥3 drugs with uncontrolled hypertension (resistant hypertension).
- Suspected secondary causes:
  - Young age (<30–40 years)
  - Historical features (i.e. obstructive sleep apnoea, phaeochromocytoma)
  - Examination findings (i.e. abdominal bruit suggesting renal artery stenosis)
  - Sudden change in BP.
- Target organ damage detected with normal BP values.
- Intolerance of medicines preventing guideline-based treatment.
- Symptomatic hypertension or hypotension.
- Labile or highly variable BP.
- Mild hypertension when it is not clear whether a patient would benefit from BP-lowering.

Box 31.7 Management of hypertensive emergencies

Presentation/ syndrome	History	Examination	Investigation of choice	Target/timeframe	First line therapies	Notes
Malignant hyper- tension	Visual disturbance, headache	Moderate–severe retinopathy		25% MAP reduction within a few hours	i.v. Labetalol, nicardipine (with retinopathy only, some consider oral atenolol sufficient)	Often associated with acute kidney injury, due to fibrinoid small-artery necrosis
Hypertensive en- cephalopathy	Visual disturbance, headache, seizures, confusion, coma	Often features moderate– severe retinopathy	MRI brain: posterior fossa oedema (PRES)	Immediate MAP reduction by 25%	i.v. Labetalol, nicardipine	
Acute aortic dissection	Tearing chest pain	Unequal arm pulses or BP Aortic valve incompetence	CT angiogram aorta, trans- oesophageal echo: dissection flap visible	Immediate SBP reduction to 100–120 mmHg *and* heart rate to 50–60 beats/min	i.v. Labetalol Once rate control is adequate, vasodilators can be added (GTN, nicardipine)	Patients with Marfan's or proximal aorta syn- dromes more commonly proceed to early surgery
Acute pulmonary oedema	Shortness of breath	Bibasal crackles, elevated jugular venous pressure	Chest X-ray: intersti- tial oedema	Immediate SBP reduction to <140 mmHg	i.v. GTN, diamorphine	Loop diuret- ics are also vasodilating and lower BP
Acute coronary syndrome	Chest pain	Diaphoretic	ECG: ST/T-wave changes Serum troponin elevated	Immediate SBP reduction to <140 mmHg	i.v. GTN, labetalol	
Pre-eclampsia	Oedema, visual disturbance, abdominal pain	Oedematous New proteinuria on string reagent testing		Immediate SBP reduction to <160 and DBP to <105 mmHg	i.v. Labetalol, nicardipine	i.v. Magnesium used to prevent/treat eclamptic seizures

CT, computed tomography; DBP, diastolic blood pressure; ECG, electrocardiography; GTN, glyceryl trinitrate; MAP, mean arterial pressure; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; SBP, systolic blood pressure.

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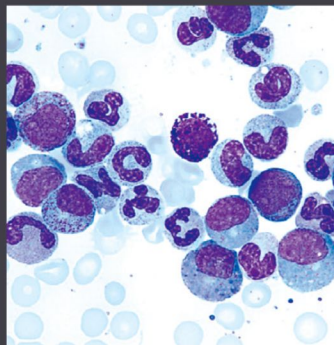# Internal Medicine
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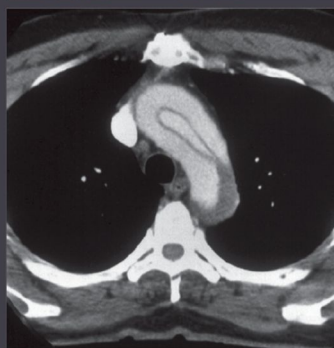
7 Hypertension[a]

C. SCOTT COLLINS, MD; CHRISTOPHER M. WITTICH, MD, PharmD

Definition

Hypertension is the most common condition seen in primary care. It can lead to myocardial infarction, stroke, renal failure, and death if not adequately treated. Normal blood pressure is defined as less than 120/80 mm Hg (Table 7.1), according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Elevated blood pressure is defined as 120 to 129/less than 80 mm Hg. Stage 1 hypertension is a blood pressure of 130 to 139/80 to 89 mm Hg; stage 2, 140 or more/90 or more mm Hg.

Initial Evaluation

Initial evaluation of hypertension should focus on 1) determining the contributing lifestyle and genetic risk factors, 2) ordering basic laboratory tests, 3) identifying and treating secondary causes of hypertension, and 4) identifying target organ damage.

Lifestyle and Individual Risk Factors

Lifestyle risk factors include family history of hypertension, black race, obesity, physical inactivity, excess sodium and alcohol intake, dyslipidemia, and type A personality traits.

Basic Laboratory Testing

Laboratory testing in the initial evaluation of hypertension is aimed at looking for end-organ damage. This should include complete blood cell count; urinalysis; analysis of glucose, creatinine, and electrolyte levels; lipid profile; and electrocardiography.

Secondary Causes of Hypertension

Diseases that cause secondary hypertension and key features of each condition are listed in Table 7.2. Physical examination and history should be tailored to ruling out these diseases.

Target Organ Damage

Target organ damage can occur as a result of hypertension (Table 7.3). Organs typically involved include heart, brain, kidney, arteries, and eyes. Physical examination should focus on these organs, looking for signs of heart failure, vascular disease, and retinopathy.

Treatment

Goals of Treatment

The goal of antihypertensive therapy is to eliminate the morbidity and death caused by disease attributable to long-term hypertension. Blood pressure treatment targets for adults aged 18 years or older have been defined in the 2017 ACC/AHA/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Geriatrics Society/American Pharmacists Association/American Society of Hypertension/American Society for Preventive Cardiology/National Medical Association/Preventive Cardiovascular Nurses Association Guideline for the Prevention, Detection, Evaluation, and

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Table 7.1 • Categories of BP in Adults[*]

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-99 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Abbreviations: BP, blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4 [of original source]); DBP, diastolic blood pressure; and SBP systolic blood pressure.

[*] Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

From Whelton PK, Carey RM, Aronow WS, Casey DR Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. pii: HYP.0000000000000065. [Epub ahead of print]; used with permission.

Management of High Blood Pressure in Adults. The hypertension management algorithm from this report defines blood pressure thresholds at which to initiate lifestyle or pharmacologic interventions and parameters for follow-up (Figure 7.1). A blood pressure target of less than 130/80 mm Hg is recommended for adults with confirmed hypertension and known cardiovascular disease. This target also is relevant for adults who have a 10% or higher 10-year atherosclerotic cardiovascular disease (ASCVD) event risk, defined by the ACC/AHA Pooled Cohort Equations. The recommendation is based on high-quality evidence. For adults with confirmed hypertension without additional markers of increased cardiovascular disease risk, a blood pressure target of less than 130/80 mm Hg may be reasonable, but this level is based on lower-quality evidence.

Lifestyle Modification

Lifestyle modifications (Table 7.4) are essential for any patient found to have increased blood pressure or any stage of hypertension. The modifications may be sufficient as initial therapy for some persons. They are adjunctive therapy for persons with persistent hypertension and should be continued throughout hypertension management.

Pharmacologic Treatment

The 2017 High Blood Pressure Clinical Practice Guideline recommends initiation of medication therapy in patients for whom lifestyle modifications are inadequate or who have increased ASCVD risk, clinical ASCVD, or stage 2 hypertension. Initial medication recommendations are based on age, race, compelling indications, and diabetes mellitus or chronic kidney disease (CKD) status.

Table 7.2 • Secondary Causes of HTN

Cause	Key Features
Endocrine	
Pheochromocytoma	Presents with headaches, diaphoresis, and palpitations
	If appropriate, screen with plasma metanephrine value
Primary aldosteronism	Presents with hypokalemia and HTN
	If appropriate, screen with aldosterone to renin ratio
Cushing disease	Presents with hyperglycemia, hypokalemia, and HTN
	If appropriate, screen with 24-hour urinary cortisol value
Hyperparathyroidism	Screen with serum calcium value
Hypothyroidism	Presents with diastolic HTN
Cardiac	
Coarctation of aorta	Examine for weak, delayed, or absent femoral pulse
	Rib notching on chest radiography
Obstructive sleep apnea	Presents in overweight persons with loud snoring, large neck circumference, morning headaches, and daytime sleepiness
	Confirm diagnosis with polysomnography
Renal	
Renal artery stenosis	Presents in smokers, persons with CAD or with new-onset HTN after age 50 years
	Examine for high-pitched systolic-diastolic abdominal bruit
Fibromuscular dysplasia	Presents in women, usually younger than 30 years without family history of HTN
Renal parenchymal disease	Check creatinine value and results of urinalysis

Abbreviations: CAD, coronary artery disease; HTN, hypertension.

Data from Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52. Epub 2003 Dec 1.

In the general hypertensive population, nonblack patients and diabetic patients without CKD should begin a treatment of thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or calcium channel blocker, alone or in combination, as initial therapy. Black patients with or without diabetes mellitus and without CKD should be given a thiazide diuretic or calcium channel blocker alone or in combination as initial therapy. All patients, regardless of race, who have CKD should receive an ACE inhibitor or angiotensin receptor

Table 7.3 • Hypertensive Target Organ Injury

Target Organ	Injury	Clinical Marker/ Diagnosis
Heart	Left ventricular hypertrophy	S_4 gallop, forceful and prolonged apical thrust
		Displacement of point of maximal intensity
		Chest radiography, ECG, echocardiography
	Angina	
	Prior myocardial infarction	
	Prior revascularization	
	Heart failure (systolic or diastolic)	History, ECG
		History
		Lung rales
		S_3 gallop
		Edema
		Chest radiography, echocardiography
Brain	Stroke	History
	Leukoaraiosis	CT or MRI
	Dementia	History
		Cognitive testing
Kidney	Chronic kidney disease	Creatinine, serum urea nitrogen, urinalysis, eGFR
Arteries	Peripheral artery disease	History of claudication
		Bruits
		Diminished pulses
Eye	Retinopathy	Funduscopic examination: generalized and focal arteriolar narrowing
		"Copper wiring" of arterioles
		Arteriovenous nicking
		Cotton-wool spots
		Microaneurysms and macroaneurysms
		Flame- and blot-shaped retinal hemorrhages
		Retinal vein occlusion
		Optic disc swelling

Abbreviations: CT, computed tomography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; S_3, third heart sound; S_4, fourth heart sound.

blocker as initial therapy alone or in combination with another drug class. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended for adults with stage 2 hypertension and an average blood pressure that exceeds 20/10 mm Hg above their blood pressure target. Adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved.

KEY FACTS

✓ Hypertension—most common condition seen in primary care; can lead to myocardial infarction, stroke, renal failure, and death if not adequately treated

✓ Target organ damage in hypertension—typically involves heart, brain, kidneys, arteries, and eyes

✓ Treatment of hypertension—blood pressure goal for adults in the general population age <60 years is <140/90 mm Hg; for adults age ≥60 years, <150/90 mm Hg. Adults of all ages with diabetes mellitus and CKD have a blood pressure goal of <140/90 mm Hg

✓ Treatment of hypertension—nonblack patients and diabetic patients without CKD should start therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker, or calcium channel blocker, alone or in combination, as initial therapy

✓ Treatment of hypertension—black patients with or without diabetes and without CKD should be given a thiazide diuretic or calcium channel blocker, alone or in combination, as initial therapy

Secondary Hypertension

Secondary causes of hypertension should be considered when the age at onset is unusual, when blood pressure changes suddenly, and when hypertension is refractory to treatment.

Renovascular Hypertension

Renovascular hypertension is a potentially curable form of secondary hypertension. Generally, renovascular hypertension is grouped into 1) renal artery stenosis and 2) fibromuscular dysplasia.

Clues that suggest renovascular hypertension include lack of a family history of hypertension, onset of hypertension before age 30 years (consideration of fibromuscular dysplasia is appropriate, especially in white women), and onset of hypertension after age 50 years (consideration of atherosclerotic renovascular disease is appropriate, especially in a smoker or a person with coronary or peripheral arterial disease). Another clue is presentation with accelerated hypertension.

The most important physical finding is an abdominal bruit, especially a high-pitched systolic-diastolic bruit in the upper abdomen or flank. However, 50% of persons with renovascular hypertension do not have this finding.

Options for the management of renovascular hypertension include interventional therapies when feasible and medical therapy for persons who are not candidates for an intervention procedure. Percutaneous transluminal angioplasty is the treatment
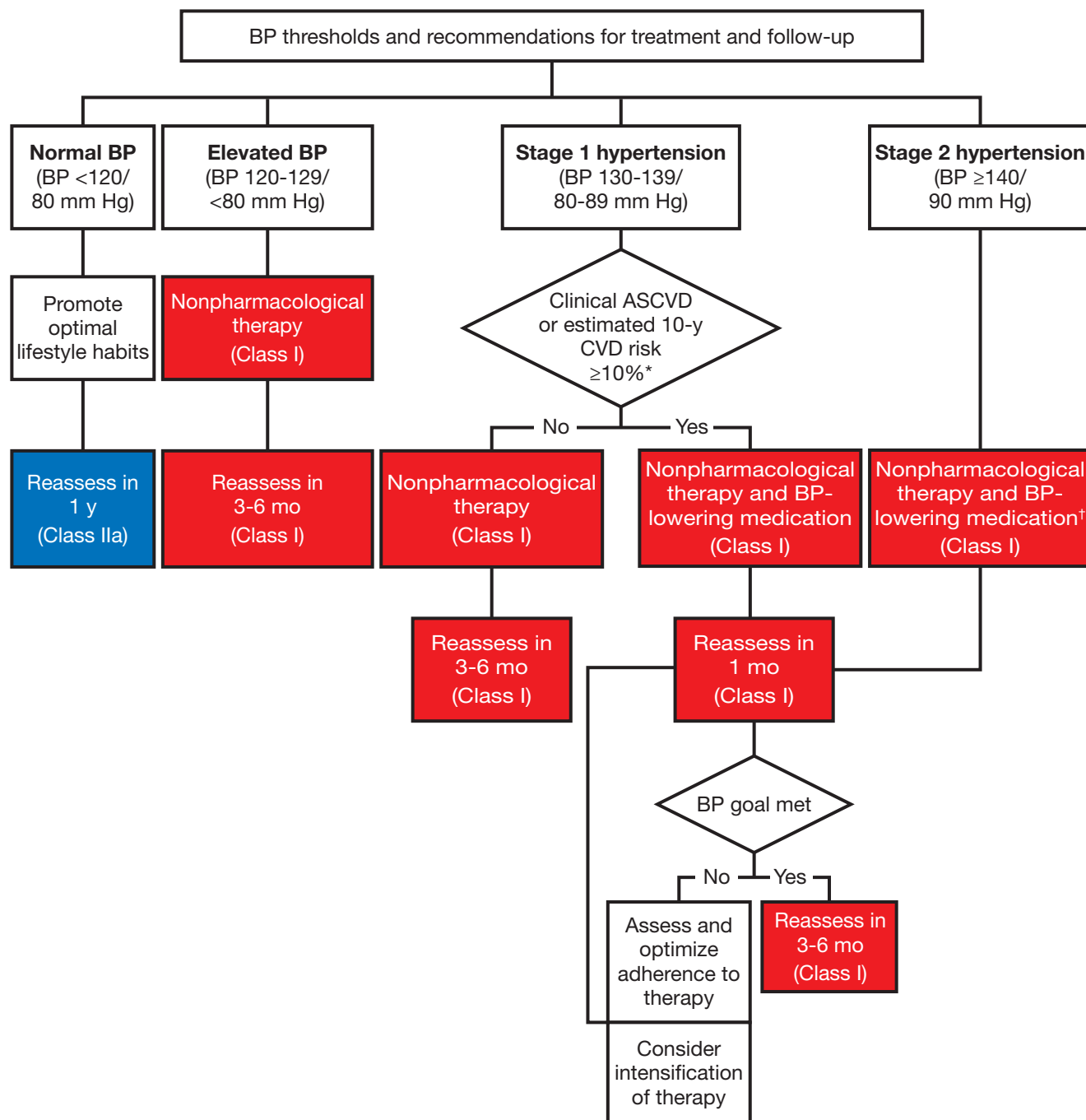
Figure 7.1. *Hypertension Management Algorithm of the 2017 High BP Clinical Practice Guideline. ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, coronary artery disease. Applying the class of recommendation and level of evidence to clinical strategies, interventions, treatments, or diagnostic testing, the class (strength) of recommendations is indicated by color. Red indicates Class I (strong); blue, Class IIa (moderate). Further detail can be found in Table 1 of the original source. * Using the American College of Cardiology/American Heart Association Pooled Cohort Equations (Circulation. 2014 Jun 24;129[25 Suppl 2]:S1-45). Of note, patients with diabetes mellitus or chronic kidney disease are automatically placed in the high-risk category. After initiation of renin-angiotensin system inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function at 2 to 4 weeks.* † *Consider initiation of pharmacologic therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP ≥160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (eg, older age, postural symptoms), identification of* white coat hypertension *or a* white coat effect, *documentation of adherence, monitoring of response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.*

(From Whelton PK, Carey RM, Aronow WS, Casey DR Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. pii: HYP.0000000000000065. [Epub ahead of print]; used with permission.)

of choice for amenable lesions caused by fibromuscular dysplasia and is an option in some cases of atherosclerotic renovascular disease. The medical treatment of renovascular hypertension is the same as that of essential hypertension.

Renal Parenchymal Disease

Renal parenchymal disease is a common secondary cause of hypertension. The major mechanisms of hypertension in renal disease include volume expansion from impaired renal elimination of salt and water, over secretion of renin, and decreased production of renal vasodilators. ACE inhibitors and angiotensin receptor blockers reduce proteinuria and high glomerular transcapillary pressures, slowing further loss of renal function. However, these medications can cause hyperkalemia and an acute decline in renal function. Modest acute decreases in renal function (<30%) should be tolerated because they are often followed by stabilization and preservation of renal function. Calcium channel blockers are effective blood pressure–lowering agents in persons with CKD. Of note, nondihydropyridine calcium channel blockers reduce proteinuria, but dihydropyridine calcium channel blockers do not.

Primary Aldosteronism

The syndrome of primary aldosteronism is characterized by overproduction of aldosterone by the adrenal glands, leading to hypertension, hypokalemia, alkalosis, hyperglycemia, and increased aldosterone levels. Prevalence estimates range from 2% to 15% of the hypertensive population.

Primary aldosteronism should be suspected in hypertensive patients who have spontaneous hypokalemia or marked hypokalemia precipitated by usual doses of diuretics. However, in many patients with primary aldosteronism, the potassium level is normal. In addition, it should be suspected in patients with an adrenal mass, a history of early-onset hypertension, or a first-degree relative who has primary aldosteronism.

Screening for primary aldosteronism is done through the use of the aldosterone to renin ratio. This ratio should be measured when the patient is not taking an aldosterone-blocking medication. In essential hypertension, the average value of the ratio is 5.5. A ratio more than 15 to 20 suggests the diagnosis of primary aldosteronism.

Treatment of primary aldosteronism can involve spironolactone, eplerenone, other antihypertensive medications, or surgery.

Pheochromocytoma

Pheochromocytoma is a tumor that causes hypertension due to excess catecholamines. Pheochromocytoma is rare; its incidence is 2 to 8 cases per 1 million persons per year. The prevalence is 0.5% among persons with hypertension.

A *rule of 10* describes the typical locations of pheochromocytomas. The rule cites that 10% are extra-adrenal; 10% of extra-adrenal gland tumors are extra-abdominal; 10% occur in children; 10% are multiple or bilateral; 10% recur after the initial resection; 10% are malignant; 10% are found in persons without hypertension; and 10% are familial.

Patients can present with paroxysms of hypertension, but most have sustained hypertension. Paroxysms can be associated with headache, diaphoresis, and palpitations. The presentation of pheochromocytoma corresponds to 5 P's: *p*ressure, *p*ain, *p*alpitations, *p*erspiration, and *p*allor. Patients can also present with symptoms mimicking an anxiety attack. In addition, pheochromocytoma can be discovered as an incidental adrenal mass on an imaging study.

Pheochromocytoma is associated with numerous outcomes. They are multiple endocrine neoplasia 2A (medullary thyroid carcinoma, pheochromocytoma, and parathyroid tumors), multiple endocrine neoplasia 2B (medullary thyroid cancer, pheochromocytoma, and neuroma), neurofibromatosis, von Hippel-Lindau disease (pheochromocytoma, retinal hemangiomatosis, cerebellar hemangioblastomas, epididymal cystadenoma, renal and pancreatic cysts, and renal cell carcinoma), and familial paraganglioma syndrome.

Diagnosis of pheochromocytoma consists of biochemical confirmation with 24-hour urine collection to measure fractionated metanephrines and fractionated catecholamines. It involves blood testing to measure plasma levels of fractionated metanephrines.

Computed tomography or magnetic resonance imaging of the abdomen and pelvis is the initial test to locate a tumor after biochemical testing has confirmed the presence of the disorder. Treatment is surgical removal. Preoperatively, administration of a phenoxybenzamine is needed to control blood pressure and cardiac rhythm. Because pheochromocytomas can recur in 10% of cases, long-term biochemical follow-up is required.

Coarctation of the Aorta

Coarctation of the aorta is a constriction of the vessel usually immediately beyond the takeoff of the left subclavian artery. It is typically detected in childhood when blood pressure in the upper extremities is increased and blood pressure in the lower extremities is decreased. Weak or delayed lower-extremity pulses can also be present. Patients can have signs of lower-extremity claudication. Dilated collateral vessels can cause bruits and characteristic rib notching on chest radiography. Treatment is surgical repair.

Obstructive Sleep Apnea

Obstructive sleep apnea is associated with hypertension that may be severe and resistant to control. Upper body obesity is a risk factor for obstructive sleep apnea and is common in hypertensive persons. The diagnosis of obstructive sleep apnea should be considered in persons who are overweight, snore loudly, have a large neck circumference, and report morning headaches and daytime sleepiness.

Other Causes of Hypertension

Cushing syndrome should be considered in the hypertensive person who has impaired fasting glucose and unexplained hypokalemia.

Hypothyroidism is associated with diastolic hypertension due to decreased cardiac output and contractility. Tissue perfusion is maintained by an increase in peripheral vascular resistance mediated by increased activity of the sympathetic nervous system.

Hyperparathyroidism may increase blood pressure directly through hypercalcemia, which increases peripheral vascular resistance, and indirectly by increasing vascular sensitivity to catecholamines.

KEY FACTS

✓ Clues suggestive of renovascular hypertension—lack of family history of hypertension, onset of hypertension before age 30 years (consideration of fibromuscular dysplasia is appropriate, especially in white women), onset of hypertension after age 50 years (consideration of atherosclerotic renovascular disease, especially in a smoker or a person with coronary or peripheral arterial disease), or presentation with accelerated hypertension

✓ Primary aldosteronism—should be suspected in hypertensive patients who have spontaneous hypokalemia or marked hypokalemia precipitated by usual doses of diuretics

✓ Pheochromocytoma—presentation corresponds to 5 P's: *p*ressure, *p*ain, *p*alpitations, *p*erspiration, and *p*allor

Special Cases of Hypertension

Pregnancy

Blood pressure typically decreases early in pregnancy (in the first 16-18 weeks) and then gradually increases. Hypertension during pregnancy is defined as a systolic blood pressure of 140 mm Hg or greater *or* a diastolic blood pressure of 90 mm Hg or greater on 2 separate occasions. Hypertension during pregnancy is associated with increased neonatal morbidity and mortality rates.

Preeclampsia is defined as a blood pressure greater than 140/90 mm Hg and proteinuria (24-hour urine protein excretion >0.3 g) that develops after the 20th week of gestation. Eclampsia is defined by seizures that occur in the presence of preeclampsia and cannot be attributed to other causes. Patients with preeclampsia can also have headache, blurry vision, epigastric pain, nephrotic-range proteinuria (>3.5 g in 24 hours), oliguria, creatinine level greater than 1.2 mg/dL, low platelet count, evidence of microangiopathic hemolytic anemia (abnormal blood smear results or increased lactate dehydrogenase value), increased liver transaminase values, and pulmonary edema.

Key Definition

Preeclampsia: *blood pressure >140/90 mm Hg and proteinuria (24-hour urine protein excretion >0.3 g) that develop after the 20th week of gestation.*

The HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count) occurs when intravascular coagulation and liver ischemia develop in preeclampsia. This syndrome can

rapidly develop into a life-threatening disorder of liver failure and worsening thrombocytopenia in the presence of only mild or moderate hypertension. The most serious complication of the HELLP syndrome is liver rupture, which is associated with high maternal and fetal mortality rates.

Hypertensive Crisis

Hypertensive crisis is defined as a systolic blood pressure less than 180 mm Hg, a diastolic blood pressure less than 120 mm Hg, or both. It can be subdivided into hypertensive urgency and emergency.

Hypertensive urgency is severe hypertension without evidence of acute target organ injury. It should be treated to decrease blood pressure to safer levels over 24 to 48 hours. This decrease can usually be achieved in the outpatient setting with oral agents.

Hypertensive emergency is severe hypertension with evidence of acute injury to target organs. It implies the need for hospitalization in the intensive care setting to immediately lower blood pressure with parenteral therapy. Parenteral medications such as sodium nitroprusside, nitroglycerin, clevidipine, nicardipine, fenoldopam, labetalol, esmolol, hydralazine, enalaprilat, and phentolamine are the available drugs of choice for hypertensive emergencies.

Key Definitions

Hypertensive urgency: *severe hypertension without evidence of acute target organ injury.*

Hypertensive emergency: *severe hypertension with evidence of acute injury to target organs.*

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HYPERTENSION, ESSENTIAL
Ronald N. Adler, MD, FAAFP ● Jeremy Golding, MD, FAAFP

🩺 BASICS

DESCRIPTION
- Essential hypertension (HTN) is HTN without an identifiable cause; it is also known as primary HTN and benign HTN. Although its importance as a risk factor for cardiovascular and other morbidity and mortality is well-established, there is significant and increasing controversy regarding recommended thresholds for diagnosis and treatment.
- HTN is defined (Joint National Committee [JNC] 8) as ≥ 2 elevated blood pressures (BPs) (1).
  - Age <60 years: systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg at ≥2 visits
  - Age ≥60 years: SBP ≥150 mm Hg and/or DBP ≥90 mm Hg at ≥2 visits
  - With diabetes or chronic kidney disease (CKD): SBP ≥140 and/or DBP ≥90 mm Hg
- Synonym(s): benign, chronic, idiopathic, familial, or genetic HTN; high BP

Geriatric Considerations
- Isolated systolic HTN is common.
- Therapy has been shown to be effective and beneficial at preventing stroke and cardiovascular morbidity and all-cause mortality (2)[A], although target SBP for seniors is higher than in younger patients (~150 mm Hg systolic), and adverse reactions to medications are more frequent. The benefit of therapy has been conclusively demonstrated in older patients for SBP ≥160 mm Hg. A target of <140/90 mm Hg may be appropriate for higher risk individuals (2) [A].
- Very elderly patients may be at particularly high risk of adverse events associated with pharmaceutical treatment of HTN.
- Strongest evidence of benefit has been shown with use of thiazide diuretics

Pediatric Considerations
- Measure BP during routine exams beginning at age 3 years.
- Defined as SBP or DBP ≥95th percentile on repeated measurements
- Pre-HTN: SBP or DBP between 90th and 95th percentile

Pregnancy Considerations
- Elevated BP during pregnancy may represent chronic HTN, pregnancy-induced HTN, or preeclampsia. angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated.
- Maternal and fetal mortality are reduced with treatment of severe HTN. Evidence is not clear for treatment of mild HTN (see topic "Preeclampsia and Eclampsia (Toxemia of Pregnancy)").
- Preferred agents: labetalol, nifedipine, methyldopa, or hydralazine

EPIDEMIOLOGY
Incidence
Incidence and prevalence is higher among men.

Prevalence
Depending on the definition used, 32–46% of adults in the United States have HTN.

ETIOLOGY AND PATHOPHYSIOLOGY
- >90% of cases of HTN have no identified cause.
- For differential diagnosis and causes of secondary HTN, see "Hypertension, Secondary and Resistant."

Genetics
BP levels are strongly familial, but no clear genetic pattern exists. Familial risk for cardiovascular diseases (CVDs) should be considered.

RISK FACTORS
Family history, obesity, alcohol use, excess dietary sodium, stress, physical inactivity, tobacco use, insulin resistance, obstructive sleep apnea (OSA)

DIAGNOSIS
- Despite more aggressive guidelines issued by the ACC/AHA in 2017, many experts consider recommendations from JNC 8 (1)[A] to retain primacy.
- Critics of the ACC/AHA guidelines note multiple methodologic concerns, especially the fact the guidelines were heavily influenced by the findings of SPRINT, which was conducted in a relatively high-risk population and therefore less applicable to many patients seen in primary care. Using thresholds of <130/80 mm Hg (as endorsed by AHA/ACC) compared to JNC 8 would result in the diagnosis of and treatment for HTN of millions more people, with unclear benefits and likely harm.
- Therefore, this chapter uses JNC 8 as its basis but focuses on recommendations that are relevant regardless of the specific guideline that is being applied. These include diagnostic considerations and using assessment of overall CV risk to guide treatment decisions.

HISTORY
- HTN is asymptomatic except in extreme cases or after related cardiovascular complications develop.
- Headache can be seen with higher BP, often present on awakening and occipital in location.

PHYSICAL EXAM
- Body mass index (BMI), waist circumference
- BP in both arms (see below for correct technique—essential to accurate diagnosis and treatment)
- Complete cardiac and peripheral pulse exam: Compare radial and femoral pulse for differences in volume and timing (evaluation for aortic coarctation (especially in young persons), subclavian stenosis)
- Funduscopic exam for arteriolar narrowing, AV compression, hemorrhages, exudates, and papilledema

DIFFERENTIAL DIAGNOSIS
- Secondary HTN: Because of the low incidence of reversible secondary HTN, special tests should be considered only if the history, physical exam, or basic laboratory evaluation suggest

a higher likelihood. Also consider for patients who prove nonresponsive to treatment (see "Hypertension, Secondary and Resistant").
- White coat HTN: elevation of BP in office setting and normal BP outside office
- Masked HTN: elevated BP at home and normal BP in office

DIAGNOSTIC TESTS & INTERPRETATION
- Incorrect BP determination is a common cause of overdiagnosis.
- Home blood pressure measurements are better associated with hard outcomes than office values, and also help to mitigate the errors of clinic measurement. Home BP measurement and monitoring should be encouraged.

ALERT
- Measuring BP:
  - Caffeine, exercise, and smoking avoided >30 minutes before measurement
  - Patient seated quietly for at least 5 minutes with feet on floor
  - Patient's arm supported at heart level
  - Correct cuff size
  - Deflate cuff slowly or use an automated device.
  - Average of two or more measurements
  - Avoid "rounding" results.
  - May leave patient alone to obtain in-office readings using an automated or patient-activated cuff
- A diagnosis of HTN should be made when:
  - Age <60 years: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg at ≥2 visits
  - Age ≥60 years: SBP ≥150 mm Hg and/or DBP ≥90 mm Hg at ≥2 visits
  - Age ≥60 years with CKD or diabetes: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg at ≥2 visits

Initial Tests (lab, imaging)
- Hemoglobin or hematocrit or complete blood count
- Complete urinalysis (may reveal proteinuria, hematuria/nephritis)
- Potassium, calcium, creatinine, and uric acid
- Lipid panel (total, high-density lipoprotein, low-density lipoprotein, triglyceride)
- Fasting blood glucose or hemoglobin A1c
- ECG to evaluate possible presence of left ventricular hypertrophy (LVH) or rhythm abnormalities

Follow-Up Tests & Special Considerations
- Special tests only if suggested by history, physical, or labs. Consider possibility of sleep apnea with high BMI.
- Ambulatory (24-hour) BP monitoring if "white coat" HTN is suspected, episodic HTN, or autonomic dysfunction
- U.K. and U.S. guidelines recognize the importance of confirmation of hypertension using home or ambulatory (24-hour) blood pressure measurement. Ambulatory measurement may be especially helpful if there is suspected autonomic dysfunction.
- CV risk assessment should be performed. The AHA/ACC risk tool likely significantly overestimates risk in many patients (50% or more, especially in multi-ethnic and older patients). Others have used a definition of "low risk" that excludes patients with a history of

CVD, diabetes mellitus, CKD, or familial hypercholesterolemia of premature coronary artery disease.

🪧 TREATMENT

GENERAL MEASURES

- The treatment discussed follows JNC 8 guidelines. Recent systematic reviews and meta-analyses of randomized trials do not support recommendations for lower-than-standard targets for the average-risk population. Potential harms of therapy must be weighed against the potential benefits.
- Treatment goals:
  - Age <60 years: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg
  - Age ≥60 years: SBP ≥150 mm Hg and/or DBP ≥90 mm Hg
  - Age ≥60 years with CKD or diabetes: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg
- More aggressive treatment may be considered in patients meeting enrollment criteria for SPRINT because aggressive treatment does show improvement in outcomes, but 61 nondiabetic patients would need to be treated (NNT) for 3 years to a goal of SBP <120 mm Hg to prevent a major cardiovascular outcome and 90 mm Hg to prevent one death.
- More intensive therapy may be considered for certain high-risk individuals. Even in secondary prevention, no firm conclusions can yet be drawn regarding the comparative effectiveness of intensive vs. standard therapy.
- Individual treatment goals should be jointly established with patients after discussion of the anticipated potential benefits and harms (shared decision making) (1)[A],(2)[A].
- Recommend lifestyle improvements, including diet, exercise, and reducing or eliminating tobacco/alcohol.
- Benefit of pharmacologic treatment of low-risk patients with class I HTN (SBP 140 to 150 mm Hg, DBP 90 to 99 mm Hg) remains uncertain, with harms including syncope, kidney injury, and electrolyte abnormalities. Individualize decisions.
- Treating patients age <60 years or with CKD or diabetes to lower-than-standard BP targets, <140/90 mm Hg, does not appear to further reduce mortality or morbidity. Individualize goal BP based on risk factors and patient preferences.
- A target SBP at or just below 150 mm Hg in patients >60 years of age is acceptable in the general population (1)[A].
- The majority of treatment benefit is attained by lowering high systolic pressures to lower pressures (e.g., from 190 mm Hg to 150 mm Hg, as compared with the benefit of lowering from 150 mm Hg to 136 mm Hg). Striving for small additional drops in BP by adding 3rd, 4th, or 5th medications to achieve a "target" is less clinically beneficial and more likely to cause adverse effects.
- Lower than standard DBP targets are not associated with decreased morbidity/mortality.

MEDICATION

- Multiple drugs at submaximal dose may achieve target BP with fewer side effects. In patients on >1 medication, divide between morning and night time for better 24-hour antihypertensive effect.
- Sequential monotherapy attempts should be tried with different classes because individual responses vary.

- Many patients will require multiple medications.
- For initial monotherapy, choose from 1 of 4 classes of medications: ACE inhibitors, ARBs, calcium channel blockers (CCBs), or diuretics (1)[A].
- Thiazide diuretics or CCB preferred as first line in the general black population
- Chlorthalidone has a longer half-life than hydrochlorothiazide (HCTZ) and is the preferred diuretic based on established trial evidence of benefit. It is a more potent antihypertensive than HCTZ.
- If concomitant conditions, choose first-line agent based on comorbidity.
- β-Blockers had been strongly recommended until recent meta-analyses. Atenolol may be particularly ineffective in reducing adverse outcomes of HTN (except in patients with left ventricle hypertrophy undergoing dialysis).
- β-Blockers often benefit patients with ischemic heart disease, atrial fibrillation, CHF, migraine, and patients with history of ST-segment elevation myocardial infarction (STEMI).
- ACE inhibitors should be used in patients with diabetes, proteinuria, atrial fibrillation, or heart failure with reduced ejection fraction (HFrEF) but not in pregnancy.
- α-Adrenergic blockers are not a first choice for monotherapy but remain as second line after combination therapy of first-line agents; might benefit males with benign prostatic hypertrophy (BPH).
- CCB could be considered in patients with isolated systolic HTN, atherosclerosis, angina, migraine, or asthma; well documented to reduce risk of stroke

First Line
- Thiazide diuretics may not be effective with creatinine clearance <30.
  - Chlorthalidone: 12.5 to 25 mg/day (longer half-life and more potent than hydrochlorothiazide but causes more hyponatremia and hypokalemia). Strongest evidence base for this medication.
  - Hydrochlorothiazide: 12.5 to 50 mg/day
  - Indapamide: 1.25 to 2.5 mg/day
  - Metolazone: 2.5 to 5 mg daily is more effective in patients with impaired renal function than other thiazides, but outcomes studies lacking.
- ACE inhibitors
  - Lisinopril: 5 to 40 mg/day
  - Enalapril: 5 to 40 mg/day
  - Ramipril: 2.5 to 20 mg/day
  - Benazepril: 10 to 40 mg/day
- CCB
  - Amlodipine: 2.5 to 10 mg/day
  - Nifedipine (sustained release): 30 to 90 mg/day
  - Diltiazem CD: 180 to 360 mg/day
  - Verapamil (sustained release): 120 to 480 mg/day
- ARBs
  - Losartan: 25 to 100 mg in 1 or 2 doses; has unique but modest uricosuric effect
  - Valsartan: 80 to 320 mg daily
  - Irbesartan: 75 to 300 mg daily
  - Candesartan: 4 to 32 mg daily
  - Renin inhibitor: aliskiren 150 to 300 mg daily
- Contraindications

- Thiazide diuretics may worsen gout.
- β-Blockers (relative) in asthma, heart block, diabetes, and peripheral vascular disease; probably should be avoided in patients with metabolic syndrome or insulin-requiring diabetes
- Diltiazem or verapamil: Do not use with systolic dysfunction or heart block. Amlodipine may cause peripheral edema.

Second Line
- Before escalating therapy, ensure that patient is adherent to prescribed regimen.
- Many may be combined. Choose additional medications with complementary effects (i.e., ACE inhibitors/ARBs with diuretic or a vasodilator with a diuretic or β-blocker). Don't combine ACE inhibitor and ARB.
- Medication-refractory HTN (see Secondary and Resistant Hypertension): Spironolactone 25 to 100 mg/day or eplerenone 50 mg once to twice daily are especially effective.
- Centrally acting α-2 agonists: clonidine 0.1 to 1.2 mg BID or weekly patch 0.1 to 0.3 mg/day, guanfacine 1 to 3 mg daily, or methyldopa 250 to 2,000 mg BID
- α-Adrenergic antagonists: prazosin 1 to 10 mg BID, terazosin 1 to 20 mg/day, or doxazosin 1 to 16 mg/day
- Vasodilators
  - Hydralazine: 10 to 25 mg QID; risk of tachycardia, so generally combined with β-blocker; also drug-induced systemic lupus erythematosus (SLE)
  - Minoxidil: rarely used due to adverse effects; may be more effective than other medications in renal failure and refractory HTN
- Metolazone and loop diuretics may be used with more severe renal impairment, but outcomes data are absent; loop diuretics (for volume overload): furosemide 20 to 320 mg/day or bumetanide 0.5 to 2 mg/day
- K^+-sparing diuretics in patients with hypokalemia while taking thiazides: amiloride 5 to 10 mg/day or triamterene 50 to 150 mg/day

COMPLEMENTARY & ALTERNATIVE MEDICINE
- Biofeedback and relaxation exercise
- Dietary supplements such as garlic have been suggested for lowering BP, but evidence is lacking.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
- Reevaluate patients q3–6mo until stable and then q6–12mo. Consider use of home BP self-monitoring; quality-of-life issues including sexual function should be considered.
- Poor medication adherence is a leading cause of apparent medication failure.
- At least annual creatinine and potassium for patients on diuretics, ACE inhibitors, and ARBs

DIET
- ~20% of patients will respond to reduced-salt diet (<100 mmol/day; <6 g NaCl or <2.4 g Na).
- Consider Dietary Approaches to Stop HTN (DASH) diet:

http://www.nhlbi.nih.gov/files/docs/public/heart/hbp_low.pdf.
- Limit alcohol consumption to <1 oz/day.

PATIENT EDUCATION
Counsel for aerobic exercise 5 days a week

COMPLICATIONS
Heart failure, renal failure, LVH, myocardial infarction, retinal hemorrhage, stroke, hypertensive heart disease, drug side effects, erectile dysfunction

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SEE ALSO

Hypertension, Secondary and Resistant; Hypertensive Emergencies; Polycystic Kidney Disease

CODES

ICD10
I10 Essential (primary) hypertension

CLINICAL PEARLS

- Treatment of HTN reduces risk with NNT to prevent one serious Major Adverse CV Events (MACE).
- Treatment decisions should be informed by BP measured by proper technique; measures outside the clinical office more predictive of CV risk.
- Overly aggressive treatment may cause significant harms, more likely and often more significant in the elderly.

HYPERTENSION, SECONDARY AND RESISTANT
George Maxted, MD

🩺 BASICS

DESCRIPTION
Uncontrolled hypertension (HTN) comprises the following entities (see "Alert" below):
- Resistant HTN: defined as blood pressure (BP) that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic, and all agents should be prescribed at optimal dose amounts (1) [C].
- Secondary HTN: elevated BP that results from an identifiable underlying mechanism (1)
- The 2017 revised American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommends a change in the classification of HTN. For the purposes of this chapter, we will be considering stage 2 HTN: systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg. The guideline is quite controversial (2). See chapter on Hypertension, Essential. Many experts still adhere to the JNC 8 guideline, which allows for a goal of <150/90 mm Hg for patients age >60 years, and disagree with classification of hypertension diagnosis for pressures below 140/90 mm Hg (3)[C].

Geriatric Considerations
- Onset of HTN in adults >60 years of age is a strong indicator of secondary HTN.
- In patients >80 years of age, consider a higher target SBP of ≥150 mm Hg. Be cautious to avoid excessive diastolic lowering.
- Elderly may be particularly responsive to diuretics and dihydropyridine calcium channel blockers.
- Systolic HTN is particularly problematic in the elderly.
- Secondary causes more common in the elderly include sleep apnea, renal disease, renal artery stenosis, and primary aldosteronism (PA).
- Noncompressible arteries (Osler phenomenon)—mostly in elderly with arteriosclerosis: Brachial and radial artery pulsations are present at high cuff pressures.

ALERT
Pseudoresistance:

- Inaccurate measurement of BP
  - Cuff too small
  - Patient not at rest; sitting quietly for 5 minutes
- Poor adherence: In primary care settings, this has been estimated to occur in 40–60% of patients with HTN.
- White coat effect: prevalence 20–40%. Do not make clinical decisions about HTN based solely on measurement in the clinic setting. Home BP monitoring and/or ambulatory BP monitoring is more reliable. See U.S. Preventive Services Task Force (USPSTF) and AHA recommendations (4).
  - Automated office blood pressure (AOBP) is the preferred method of measurement. If AOBP is not possible, home blood pressure measurement (HBPM) is preferred when

making decisions about treatment.
- Inadequate treatment

EPIDEMIOLOGY
- Predominant age: In general, HTN has its onset between ages 30 and 50 years. Patients with resistant HTN are more likely to experience the combined outcomes of death, myocardial infarction, congestive heart failure (CHF), stroke, or chronic kidney disease.
- Depending on etiology, age of onset can vary. Age of onset <20 or >50 years increases likelihood of a secondary cause for HTN.
- The strongest predictors for resistant HTN are age (>75 years), presence of left ventricular hypertrophy (LVH), obesity (body mass index [BMI] >30), and high baseline SBP. Other predictors include chronic kidney disease, diabetes, living in the southeastern United States, African American race (especially women), and excessive salt intake.

Prevalence
- Prevalence of resistant HTN is unknown. National Health and Nutrition Examination Survey analysis indicates only 53% of adults are controlled to a BP of <140/90 mm Hg. The most common cause of apparently resistant hypertension is likely medication nonadherence.
- Secondary HTN occurs in about 5–10% of adults with chronic HTN.

ETIOLOGY AND PATHOPHYSIOLOGY
- Obstructive sleep apnea (25–50%)—results of interventions have been mixed
- Primary hyperaldosteronism (8–20% of resistant HTN cases)
- Chronic renal disease (1–2% of hypertensives)
- Renovascular disease (0.2–0.7%, up to 35% of elderly, 20% of patients undergoing cardiac catheterization)
- Cushing syndrome (<0.1%)
- Pheochromocytoma (0.04–0.1% of hypertensives)
- Other rare causes: hyperthyroidism, hyperparathyroidism, aortic coarctation, intracranial tumor
- Drug-related causes
  - Medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs) (may also blunt effectiveness of angiotensin-converting enzyme inhibitors), decongestants, stimulants (e.g., amphetamines, attention deficient hyperactivity disorder [ADHD] medications), anorectic agents (e.g., modafinil, ephedra, guarana, ma huang, bitter orange), erythropoietin, natural licorice (in some chewing tobacco), yohimbine, glucocorticoids
  - Oral contraceptives: unclear association; mainly epidemiologic and with higher estrogen pills
  - Cocaine, amphetamines, other illicit drugs; drug and alcohol withdrawal syndromes
- Lifestyle factors: Obesity and dietary salt may negate the beneficial effect of diuretics. Excessive alcohol may cause or exacerbate HTN. Physical inactivity also contributes.

RISK FACTORS
A recent large cohort study revealed that those with resistant HTN (16.2%) were more likely to be male, Caucasian, older, and diabetic. They were also more likely to be taking β-blockers, calcium channel blockers, and α-adrenergic blockers compared with other drug classes. Factors predictive of resistant or secondary HTN: female sex, African American race, obesity, diabetes, worsening of control in previously stable hypertensive patient, onset in patients age <20 years or >50 years, lack of family history of HTN, significant target end-organ damage, stage 2 HTN

(SBP >160 mm Hg or DBP >100 mm Hg), renal disease, and alcohol or drug use

GENERAL PREVENTION

The prevention of resistant and secondary HTN is thought to be the same as for primary or essential HTN: Adopting a Dietary Approaches to Stop Hypertension (DASH) diet, a low-sodium diet, weight loss in obese patients, exercise, limitation of alcohol intake, and smoking cessation may all be of benefit. Relaxation techniques may be of help, but data are limited.

DIAGNOSIS

HISTORY

- Ask or review at every visit: SANS mnemonic: (i) Salt intake, (ii) Alcohol intake, (iii) NSAID use, (iv) Sleep (author's suggestion, based on reference listed) (2)
- Review home BP readings; consider ambulatory BP monitoring.
- History will vary with etiology of HTN.
  - OSA: loud snoring while asleep, daytime somnolence
  - Pheochromocytoma: episodes of headache, palpitations, sweating
  - Cushing syndrome: weight gain, fatigue, weakness, easy bruising, amenorrhea
  - Increased intravascular volume: swelling

PHYSICAL EXAM

- Ensure that the BP is measured correctly. The patient should be sitting quietly with back supported for at least 5 minutes before measurement. Proper cuff size: bladder encircling at least 80% of the arm. Support arm at heart level. Minimum of two readings at least 1 minute apart. Check BP in both arms. Also check standing BP for orthostasis.
- The USPSTF recommends "obtaining measurements outside of the clinical setting for diagnostic confirmation." Attention to findings related to possible etiologies: renovascular HTN: systolic/diastolic abdominal bruit; pheochromocytoma: diaphoresis, tachycardia; Cushing syndrome: hirsutism, moon facies, dorsal hump, purple striae, truncal obesity; thyroid disease: enlarged thyroid, tremor, exophthalmos, tachycardia; coarctation of the aorta: upper limb HTN with decreased or delayed femoral pulses
- Check pulses, heart auscultation, legs for edema

DIFFERENTIAL DIAGNOSIS

Pseudoresistance

DIAGNOSTIC TESTS & INTERPRETATION

- ECG performed as part of the initial workup; LVH is an important marker of resistant HTN.
- Sleep study if history and physical indicate. The Epworth Sleepiness Scale is recommended.
- Home-based polysomnography has been shown to be accurate in screening for OSA. Overnight oximetry is not helpful.

Initial Tests (lab, imaging)

Initial limited diagnostic testing should include urinalysis, CBC, potassium, sodium, glucose, creatinine, lipids, thyroid-stimulating hormone (TSH), and calcium. 50% of patients with hyperaldosteronism may have normal potassium levels.
- Imaging tests listed are necessary only if history, physical, or lab data indicate.

- Abdominal US: if renal disease is suspected
- Duplex ultrasonography may be the preferred test for renovascular disease. MR angiography (MRA) of renal vasculature is sensitive but has low specificity and potentially more harmful. Conventional catheter angiography or CT angiography may be required to confirm the diagnosis.
- Adrenal "incidentaloma" frequently arises in this era of multiple CT studies. If present in the setting of resistant HTN, consider hyperaldosteronism or hyperadrenal corticoid states.

Follow-Up Tests & Special Considerations
Further testing for PA may be considered.
- Empiric treatment with an aldosterone inhibitor may be preferable and more clinically relevant: spironolactone or eplerenone. Amiloride may be more effective in African Americans.
- Plasma aldosterone-to-renin ratio (ARR) is the preferred lab test, but the test is difficult to perform and interpret properly. Consult your reference lab and interpret results with caution.
  - Further testing for pheochromocytoma: plasma metanephrines
  - Other tests to consider for resistant or secondary HTN: 24-hour urine for free cortisol, calcium, parathyroid hormone (PTH), overnight 1-mg dexamethasone suppression test, urine toxicology screen

Diagnostic Procedures/Other
Consider 24-hour ambulatory BP monitoring (ABPM), especially if white coat effect is suspected. Home BP monitor results predict mortality, stroke, and other target organ damage better than office BP. Optimal protocol involves two paired measurements: morning and evening (four measurements) over 4 to 7 days.
- Oscillometric, electronic, upper arm, fully automatic device with memory: average multiple readings over several days
- See http://www.dableducational.org/ for validated monitors.

TREATMENT
- Treatment modality depends on etiology of HTN. Please see each etiology listed for information on proper treatment.
- Emphasize adherence to JNC 8 and/or AHA/ACC guidelines, with emphasis on lifestyle modification (2,3)[C].
  - Obese patients, African Americans, and elderly may be particularly responsive to diuretics.
  - Tolerance to diuretics may occur: long-term adaptation to thiazides or the "braking effect." Consider increasing the dose of thiazide or adding an aldosterone inhibitor.
- Treatment specific to certain secondary etiologies
  - PA: aldosterone receptor antagonist: spironolactone or eplerenone
  - Cushing syndrome: aldosterone receptor antagonist
  - OSA: continuous positive airway pressure (CPAP) ± oxygen, surgery, weight loss
    - Mandibular advancement devices may be equally effective in some patients.
  - Nocturnal hypoxia: oxygen supplementation
  - Renal sympathetic denervation is controversial as current approaches have largely failed to demonstrate clinical benefit. New techniques/approaches are under study.

- The treatment of atherosclerotic renal artery stenosis (ARAS) is controversial. A recent meta-analysis again questions the value of percutaneous stenting (5)[B].

MEDICATION

- Follow treatment guidelines and algorithms by JNC 8 and AHA/ACC/CDC, understanding the differences between them (2,3)[C].
- Adding a medication to the regimen may have greater efficacy than increasing the dose of medications (see JNC 8 management algorithm option B) (3).
- Aldosterone antagonists may offer significant benefit (6)[B].
- Central-acting agents (e.g., clonidine) are effective at reducing BP, but outcome data are lacking.

ALERT

- Agents specific for treatment of HTN emergencies should be initiated in those situations, in which immediate BP reduction will prevent or limit end-organ damage (see "Hypertensive Emergencies").
- Renovascular HTN: Angioplasty is the treatment of choice for fibromuscular dysplasia of a renal artery.
- The recent CORAL study concluded that in patients with atherosclerotic renovascular disease and HTN, renal artery stenting did not improve outcomes over medical therapy alone.
- Referral to an HTN specialist or clinic: Retrospective studies indicate improved control rates for patients with resistant HTN referred to special HTN clinics.

First Line

- For non-black patients: thiazide diuretics, ACEi or angiotensin receptor blocker (ARB) (not both), calcium channel blocker (CCB)
- For black patients: thiazide diuretics, CCBs. Hydralazine and isosorbide mononitrate or dinitrate are options.

Second Line

Combine thiazide diuretic with ACEi, ARB, or CCB or add a K^+-sparing diuretic. β-Blockers—especially if compelling indication such as ischemic heart disease or CHF—migraine and tachyarrhythmias may also be indications.

Third Line

Add agent not used in second line; if this does not adequately lower BP, initiate workup for secondary causes (chronic NSAID use, alcohol abuse, recurrent aphthous stomatitis, etc.).

ADDITIONAL TREATMENT

Nondrug interventions, other than standard lifestyle modifications, may be helpful.

COMPLEMENTARY & ALTERNATIVE MEDICINE

The University of Wisconsin Integrative Medicine program has an excellent handout and patient information.

ADMISSION, INPATIENT, AND NURSING CONSIDERATIONS

Hospitalization may be necessary for hypertensive urgency or emergency general measures.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Encourage aerobic activity of 30 min/day, depending on patient's condition.

DIET
- Reduced salt may lower BP in some patients.
- Recommend the Mediterranean diet or DASH.

PATIENT EDUCATION
Home BP monitoring is recommended.

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- Bell KJL, Doust J, Glasziou P. Incremental benefits and harms of the 2017 American College of Cardiology/American Heart Association high blood pressure guideline. JAMA Intern Med. 2018;178(6):755–757.
- Department of Family Medicine and Community Health, University of Wisconsin School of Medicine and Public Health. Non-pharmaceutical therapy for hypertension. https://www.fammed.wisc.edu/integrative/resources/modules/hypertension/.

- Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? Eur Heart J. 2014;35(19):1245–1254.

SEE ALSO

Aldosteronism, Primary; Coarctation of the Aorta; Cushing Disease and Cushing Syndrome; Hyperparathyroidism; Hypertension, Essential; Hyperthyroidism; Pheochromocytoma

CODES

ICD10

- I15.9 Secondary hypertension, unspecified
- I15.8 Other secondary hypertension
- I15.0 Renovascular hypertension

CLINICAL PEARLS

- Onset of HTN in adults >60 years of age is a strong indicator of secondary HTN.
- Common causes of resistant HTN: OSA, excessive salt intake, medication nonadherence, alcohol, NSAIDs
- Common secondary causes include sleep apnea, renal disease, renal artery stenosis, and PA.
- Aldosterone inhibitors should be considered in all cases of resistant HTN.
- Home BP monitoring predicts outcomes better than office monitoring of BP.