The calculated creatinine clearance should be multiplied by 0.85 for females when the serum creatinine concentration is less than 5 mg/dL and renal function is not rapidly changing.

Using Clearance for Dose Adjustment

The dose of a drug used in renal insufficiency ($dose_{D\text{-}RI}$) is proportional to the dose used with normal renal function ($dose_D$) in the same ratio as clearance of the drug in renal insufficiency ($Cl_{D\text{-}RI}$) to clearance with normal renal function (Cl_D). By rearranging, $dose_{D\text{-}RI}$ is defined as:

$$Dose_{D\text{-}RI} = dose_D \times [Cl_{D\text{-}RI}/Cl_D] \quad (10)$$

The $Cl_{D\text{-}RI}$ can be estimated by multiplying Cl_D by the ratio of the creatinine clearance in renal insufficiency ($Cl_{cr\text{-}RI}$) over Cl_{cr} with normal renal function:

$$Cl_{D\text{-}RI} = Cl_D \times [Cl_{cr\text{-}RI}/Cl_{cr}] \quad (11)$$

As shown in Equation 3, total clearance is the sum of clearance by renal and nonrenal (typically hepatic) mechanisms. Any nonrenal clearance is assumed to remain normal, and only the renal clearance is adjusted, with total clearance being reduced only to the extent that renal clearance is reduced. The dose may be calculated from the total (adjusted) clearance and the desired plasma concentration by either Equation 7 or Equation 8.

However, the calculated dose is only an initial guide to the needed dose. By monitoring the drug response or the plasma drug concentration at various times after initial dosing, further dose adjustments can be made as necessary. From a practical perspective, most clinical dose adjustments in the presence of renal dysfunction can be guided by published tables based on changes in glomerular filtration rate and the effectiveness of dialysis in removing the drug. Computerized decision support systems are particularly effective in guiding medication dosing for inpatients with renal insufficiency.

Loading Dose in Renal Insufficiency

For drugs that are typically administered with a loading dose in patients with normal renal function, the same approach can be used in patients with renal insufficiency to ensure that the desired concentration is achieved rapidly. For drugs typically administered without a loading dose, the prolonged half-life that results from renal insufficiency may delay the time required to reach a steady state. In this setting, a loading dose (equal to the amount needed to reach steady state with normal renal function) should be followed by lower or less frequent maintenance doses.

Liver Disease

Although many drugs are biotransformed in the liver, no useful laboratory test can guide dose adjustments. If the liver's capacity to produce protein (reflected by a low albumin concentration and prolonged prothrombin time) is reduced significantly, the clearance of drugs metabolized by the cytochrome P-450 enzymes is probably reduced as well.

One special situation that can develop with chronic liver disease and may require dose adjustment is portal hypertension with a portacaval shunt (Chapter 139). In this situation, hepatic blood flow decreases and hepatic clearance also decreases, thereby reducing the first-pass effect and resulting in higher concentrations of drug reaching the systemic circulation. Drugs with a large hepatic extraction that are typically administered orally (e.g., propranolol to lower portal vein pressure) may appear in the systemic circulation at higher, potentially toxic concentrations.

Hemodynamic Diseases

Decreased cardiac output and hypotensive conditions lead to decreased perfusion of the organs, including those responsible for eliminating drugs. The drug dose can be adjusted for decreased renal perfusion by the use of creatinine clearance. The effect of decreased hepatic blood flow on pharmacokinetics is more difficult to assess. For drugs that have a high hepatic extraction (e.g., lidocaine), decreased hepatic blood flow suggests a need for dose reduction.

Altered hemodynamics also may affect the distribution of selected drugs. Drugs that have a relatively large volume of distribution (e.g., lidocaine) may be affected by conditions leading to hypotension, such as shock, thereby resulting in a decrease in the apparent volume of distribution and a need to reduce the loading dose to avoid potentially toxic drug levels.

In general, in the setting of severely compromised hemodynamics, it is advisable to be conservative and to avoid potentially toxic loading and maintenance doses. Drug levels and the clinical status should be monitored closely, and drug doses should be adjusted as necessary.

TABLE 25-1 GENERAL RECOMMENDATIONS FOR DRUG USE IN ELDERLY PATIENTS

- Clearance of drugs eliminated by the kidneys may be reduced by 50%.
- Drugs eliminated primarily by the liver typically do not require dose adjustments for age, except for drugs with high hepatic clearances, which may be affected by the age-related decrease in hepatic blood flow.
- Because of the potential for increased target organ sensitivity in elderly people, only the lowest effective dose should be used.
- Frequent reviews of the patient's drug history should be conducted, including both prescription and over-the-counter medications, keeping in mind the increased potential risk for drug interactions and adverse drug responses.

APPROACH TO DRUG OVERDOSE

The pharmacokinetic principles discussed earlier can be used to determine the best approach for drug removal in the setting of a drug overdose (Chapter 96), particularly if hemodialysis or hemoperfusion remove a substantial fraction of the total body load of drug. For drugs with a large volume of distribution (e.g., warfarin), only a small amount can be removed because clearance affects only the amount of drug present in the plasma, and a large portion of the drug is outside the plasma compartment. Similarly, for a drug with high clearance value (e.g., metformin), hemoperfusion may increase the overall clearance only minimally and is not indicated.

DRUG USE IN ELDERLY PATIENTS

Administering drugs to elderly patients (Chapter 24) is perhaps the most challenging area of adult therapeutics because of several factors: the increasing likelihood of multiple illnesses, often with multisystemic involvement; the need for these patients to take multiple drugs (often prescribed by different physicians); and the increasing probability of altered pharmacokinetics and pharmacodynamics. These factors together contribute to a significantly increased frequency of drug interactions and adverse drug responses in this group of patients (Table 25-1).

Pharmacokinetic Changes with Age

Pharmacokinetic changes can be secondary to the general physiologic effects of aging, such as alteration in body composition, or to specific changes in pharmacokinetically important organs (e.g., kidneys, liver). The distribution of drugs tends to change dramatically with age, mainly because of changes in body composition. Most typical is the increase in total body fat, with the accompanying decrease in lean body mass and total body water. The concentration of plasma proteins may also change; in particular, the albumin level may decrease as the liver ages. For water-soluble drugs that are not bound to plasma proteins, the apparent volume of distribution is reduced; in contrast, for lipid-soluble drugs, the volume of distribution is increased. Changes in metabolism also accompany aging, but these changes alone do not typically account for altered pharmacokinetics.

The clearance of many drugs is decreased in the elderly because cardiac output and blood flow to the kidneys and liver may be decreased. Glomerular filtration rate may be reduced by 50%. Hepatic elimination of drugs is less affected, except for drugs with a high hepatic clearance (e.g., lidocaine). The elimination half-life of many drugs is increased with aging as a consequence of a larger apparent volume of distribution and a decreased hepatic or renal clearance (see Equation 5).

Pharmacodynamic Changes with Age

Pharmacodynamic changes are a result of changes in the responsiveness of the target organ. Elderly individuals typically require lower drug doses, even if the pharmacokinetics are little changed. For example, antianxiety drugs and drugs from the sedative-hypnotic class may produce increased central nervous system depression in elderly patients at concentrations that are well tolerated in younger adults.

INTERACTIONS AMONG DRUGS

Because patients are typically treated with multiple agents, even for a single disease, the possibilities for drug interactions are great. Many clinically important drug interactions typically involve a drug with a low therapeutic index (e.g., warfarin) and an easily detectable pharmacologic effect (e.g., bleeding), such that a small increase in the amount of drug produces a significant effect (toxicity).

It is difficult to assess the prevalence of drug interactions in either the inpatient or the ambulatory setting, particularly because no formal and comprehensive

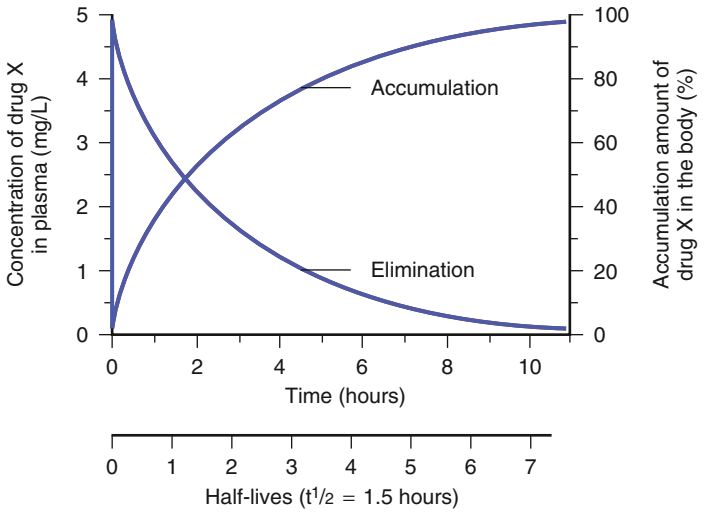

FIGURE 25-3. Representative plot of the mirror-image relationship between the elimination of drug (after drug is discontinued) and the accumulation of drug (during infusion). The plot shows the concentration on the left *y*-axis and time on the upper *x*-axis. The lower *x*-axis shows the time in half-lives, and the *y*-axis on the right shows the percentage of drug in the body. After five half-lives, elimination is essentially complete, and accumulation is essentially at a steady state.

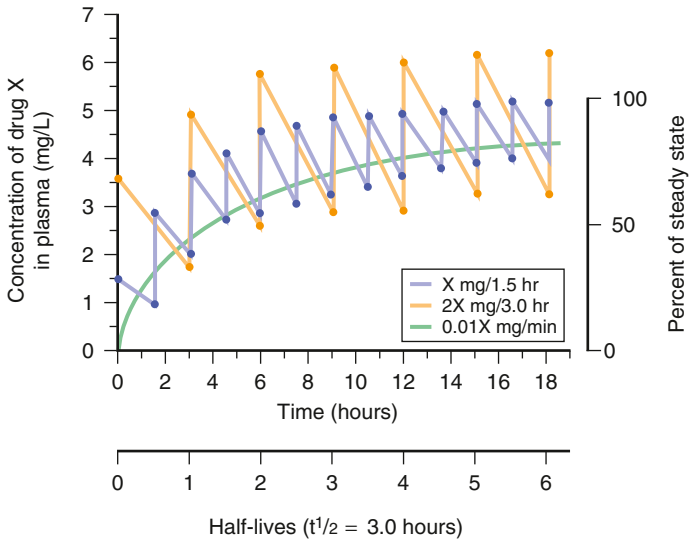

FIGURE 25-4. Accumulation of drug over time, approaching a steady state. Time is depicted in hours (upper *x*-axis) and half-lives (lower *x*-axis, showing that steady state is reached in approximately five half-lives). The *green line* depicts the pattern produced by an infusion of a hypothetical drug at a dose of 0.01X. The *orange line* shows the pattern resulting from oral administration of a 2X dose every 3 hours, and the *blue line* represents the pattern produced by oral administration of dose X every 1.5 hours.

Determining Drug Accumulation

Continuing to administer a drug, either as a prolonged infusion or as repeated doses, results in accumulation until the drug level reaches a steady state at which plasma and tissue levels remain constant because the amount of drug being administered equals the amount being eliminated. The elimination half-life determines not only the time course of drug elimination but also the time course of drug accumulation (Fig. 25-3). As with drug elimination, five half-lives is the approximate time needed to reach steady state during drug accumulation. Whereas drugs with short half-lives accumulate rapidly, drugs with long half-lives require a longer time to accumulate, thereby potentially delaying the achievement of therapeutic levels. For drugs with long half-lives, a loading dose may be needed to obtain rapid drug accumulation and a more rapid therapeutic effect.

With each change in drug dose or rate of infusion, a change in steady state occurs. Although it is not obvious for drugs with short half-lives, the effects of dose adjustments for drugs with longer half-lives are delayed, and the time varies directly with the drug's half-life.

Using a Maintenance Dose

After steady state is reached in approximately five half-lives, with either a continuous infusion or intermittent doses, the rate of drug administered equals the rate of drug eliminated. For an intravenous drug, the administration rate is the infusion rate (I); for a drug administered by another route (e.g., orally), the administration rate is the dose per unit of time (D/t). Equation 7 shows that the rate of elimination (total) equals $Cl_{tot} \times C_p$. With an intravenously administered drug, because the infusion rate equals the elimination rate at steady state, it follows that

$$I = Cl_{tot} \times C_p \quad (7)$$

Similarly, with an orally administered drug, the dose administered per unit of time equals the elimination rate at steady state, with the result that

$$D/t = Cl_{tot} \times C_p \quad (8)$$

These equations show the direct relationship between the dose and the resultant plasma concentration at steady state. This relationship is independent of the distribution of the drug. By use of these equations, it is possible to determine the infusion rate or the interval and dose needed to achieve and maintain a specified drug concentration in the plasma.

When a drug is administered intermittently, it approaches steady-state concentration over time, with a pattern similar to that observed with continuous infusion (Fig. 25-4). With intermittent drug administration, such as with an oral dose, the drug concentration fluctuates; the magnitude of fluctuation between the peak and trough concentrations depends on the interval of administration, drug half-life, absorption characteristics, and site of administration. As the intervals decrease below the half-life, the fluctuation decreases and approaches the curve produced by an intravenous infusion. With timed-release formulations, orally administered drugs reach peak concentration more slowly but persist longer in the plasma.

Decreasing the Drug Level

At times, it may be necessary to decrease the plasma drug level while maintaining therapy (e.g., when signs of toxicity become apparent or a potentially dangerously high concentration of drug is noted; see later). The most effective and rapid response is to discontinue the drug; the length of time for which the drug is discontinued is determined by the estimated half-life of the drug in the specific patient. After discontinuation of the drug for a time based on its half-life, the total clearance (Cl_{tot}) of the drug can be used to determine what infusion rate (I, Equation 7) or dose and interval (D/t, Equation 8) must be used to achieve the new desired concentration (C_p).

Effect of Dose Increases on Elimination Kinetics

Not all drugs behave the same when the dose is increased. For most drugs, elimination follows first-order or linear kinetics; the amount of drug eliminated is directly proportional to the concentration of drug in the plasma (Fig. 25-5A). However, a few drugs have a different pattern of elimination. For example, ethanol, phenytoin and aspirin have dose-dependent, nonlinear saturation kinetics. As the dose of drug increases and the concentration of drug in the plasma rises, the relative amount of drug being eliminated falls (i.e., the clearance decreases) until the rate of drug metabolism is at its maximum. At this point, drug elimination is said to be zero order, and the drug concentration in plasma starts to increase much more (no longer linearly) with each subsequent increase in dose (Fig. 25-5B).

DRUG MONITORING AS A GUIDE TO THERAPY

Although published pharmacokinetic data (usually population averages) are useful to determine initial drug dosing, modification of the dose may be needed in an individual patient. For some drugs (e.g., certain antihypertensive agents or anticoagulants), the therapeutic effects (e.g., blood pressure or coagulation) can be quantified easily over a range of concentrations, thereby permitting adequate drug adjustment. For many other drugs (e.g., some antiarrhythmic or antiseizure medications), therapeutic effects over a range of concentrations are not readily detectable. With these drugs, the plasma concentration may provide further guidance in optimizing therapy if the plasma concentration of the drug is a reflection of its concentration at the site of action and the drug effects are reversible. A third, much smaller group of drugs produces irreversible effects (e.g., aspirin inhibition of platelet aggregation). With these drugs, plasma drug concentration does not correlate with drug effect, and drug monitoring is not useful.

To use drug concentration as a guide to therapy, the range of effective but safe concentrations, or the *therapeutic window*, is usually determined from a dose-response curve generated from a population of patients who have been examined closely for therapeutic and toxic effects (Fig. 25-6). The *therapeutic*

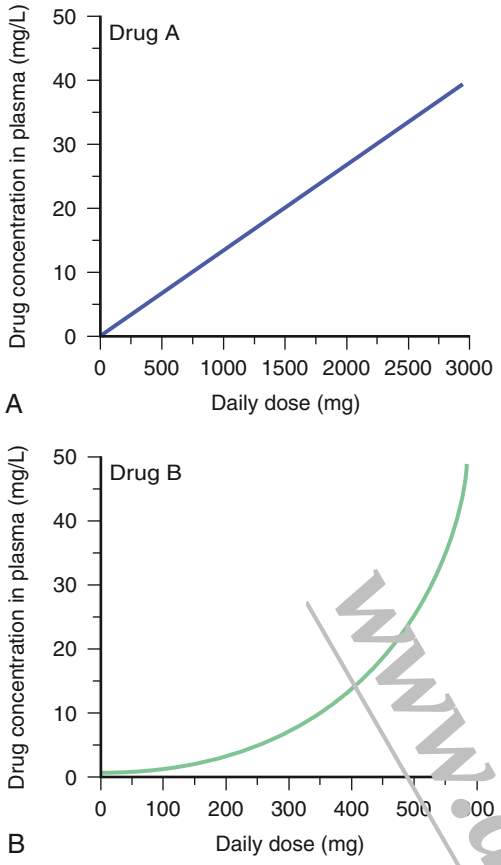

FIGURE 25-5. **Effect of increasing the dose of a drug on its serum concentration. A, Drug A follows first-order or linear kinetics. B, Drug B follows zero-order or nonlinear (or saturable) kinetics.**

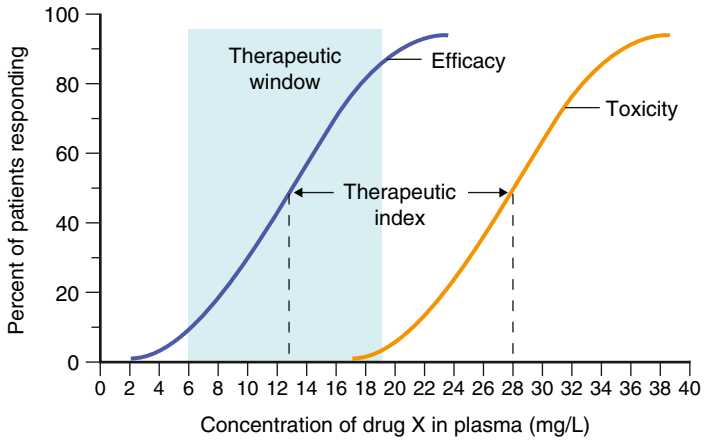

FIGURE 25-6. **Pattern produced in a dose-response population study in which both effect and toxicity are measured. The therapeutic window is shown as the range of therapeutically effective concentrations, which includes most of the efficacy curve and less than 10% of the toxicity curve. The therapeutic index is calculated by dividing the 50% value on the toxicity curve by the 50% value on the efficacy curve.**

index, which is a useful measure of drug toxicity, is calculated by dividing the 50% value from the toxicity curve by the 50% value from the efficacy curve. Because these curves are generated from population data, the values may not be applicable to all individuals.

Drug monitoring is especially useful when a drug is used to treat a serious or life-threatening disease and it is essential to avoid inadequate doses (because a therapeutic effect is often critical) as well as excessive doses (because of the risk for toxicity). In contrast, it is not necessary to assay levels of drugs used to treat noncritical diseases (when inadequate treatment is not a serious problem) or for which the therapeutic index is large (when relative overtreatment is not likely to produce toxicity).

Problems with Interpreting Drug Concentration

The time of blood collection, perhaps more than any other factor, contributes to the misinterpretation of drug levels. If sampling is performed too early, while the drug is still in the distribution phase, the drug level may be high and not reflect drug concentration at the site of action. It is therefore important to sample after the distribution phase.

For many drugs administered intermittently, such as intravenous antibiotics (e.g., vancomycin), a trough level, which is obtained immediately before the next dose is administered, is most useful for making decisions about dose adjustments. For drugs administered by infusion or intermittently at short intervals, the best time to draw blood is during steady state.

Protein binding is another major factor that contributes to the misinterpretation of drug levels. Free drug (not bound to protein and able to equilibrate with tissues and to interact with the site of action) is the critical drug concentration when therapeutic decisions are being made. Many drugs are tightly bound to plasma protein, however. Many commonly used drugs (e.g., aspirin, carbamazepine, and phenytoin), have protein binding of more than 75%, so assessment of the total drug level may not be helpful. Unfortunately, assessment of the "true" free drug concentration also may be inaccurate, particularly if the fraction of drug bound to protein varies. In addition, the drug's binding may be decreased by disease or by other drugs, thereby leading to increased unbound drug levels that alter the interpretation of the measured drug concentrations. Kidney and liver disease can change the binding of certain drugs (e.g., phenytoin) to protein because of a decrease in protein (e.g., decreased albumin, as in nephrotic syndrome or liver disease) or as a result of competition for protein binding by endogenously produced substances (e.g., uremia in kidney disease, hyperbilirubinemia in liver disease). Similarly, other drugs being administered may compete for binding to protein. A major problem secondary to these changes in protein binding is that free drug is not typically measured in many of the common drug assays used by clinical laboratories. Lastly, changes in drug binding to protein can affect the pharmacokinetics of the drug; the volume of distribution increases as protein binding decreases.

The usefulness of a drug assay is also limited by physiologic changes that may alter the response at a particular drug concentration. An example is the response produced by increasing levels of phenytoin in the presence of reduced protein binding (e.g., with hypoalbuminemia or renal impairment), where changes in phenytoin's blood concentration will be exaggerated.

Tolerance, which is a reduced response to a given concentration of drug with continued use, is commonly observed with the continued use of opioids (e.g., in terminal cancer patients). After long-term administration, the same drug concentration is no longer associated with the same pain relief. Positive (placebo) or negative (nocebo) effects may also be associated with many drugs and may mimic their known benefits or toxicities.[2]

ADJUSTMENTS OF DRUG DOSE WITH DISEASE

Kidney Disease

The main questions to be answered when determining whether a drug dosage needs to be adjusted in the setting of kidney disease are: is the drug primarily excreted through the kidneys, and are increased drug levels likely to be associated with toxicity? If the answer to both questions is yes, a drug is likely to accumulate and become toxic as renal clearance decreases unless the drug dose is reduced.

To obtain the desired concentration over time in the presence of decreased clearance, adjustments can be made by decreasing the dose while maintaining the dose interval, maintaining the dose but increasing the interval between doses, or a combination of both (E-Table 25-2). With these adjustments, it may be possible to achieve an average concentration similar to that obtained with normal renal function, but there may be concomitant marked changes in the magnitude of peak and trough values. In choosing the type of drug adjustment, the clinician should consider not only the therapeutic index of the drug but also whether an effective concentration must be achieved quickly and maintained within a narrow range (i.e., maintaining an average drug concentration and avoiding trough levels at which the drug is ineffective); and whether toxicity is associated with elevated (i.e., peak) drug concentrations.

Renal drug clearance correlates with creatinine clearance (whether the drug uses glomerular filtration or tubular secretion), so any adjustment of drug dose in kidney disease can use the creatinine clearance to estimate the dose needed. The creatinine clearance (Cl_{cr}), which is used as an estimate of glomerular filtration rate, may be calculated directly from the serum creatinine concentration by the following equation:

$$Cl_{cr} = [(140 - \text{age}) \times \text{weight (kg)}] / [72 \times \text{serumcreatinine (mg/dL)}] \quad (9)$$

EFFECTS OF AGING ON SPECIFIC ORGANS AND SYSTEMS

CARDIOVASCULAR SYSTEM

Between the ages of 20 and 80 years, left ventricular systolic function does not change, but the left ventricle gradually thickens. The result is that left ventricular filling in early diastole declines by 50%, and ventricular filling becomes more dependent on atrial contraction (Chapter 41).[3] Although atherosclerosis is the most important cause of symptomatic cardiac disease in elderly people, the age-associated vascular stiffness results in an age-related increase in heart failure despite normal systolic function (Chapter 45). With the gradual loss of up to 90% of sinus node pacemaker cells by the age of 80 years, both the resting heart rate and the maximal heart rate with exercise decline. Conduction system dysfunction contributes to an increase in the prevalence of atrial fibrillation, which is seen in about 4% of community-dwelling older individuals (Chapter 52) and can develop in up to one third of the elderly after surgery (Chapter 401). Heart valves thicken and stiffen, and the prevalence of aortic stenosis and mitral annular calcifications rises (Chapter 60), often causing heart murmurs.

Stiffening of the aorta causes an increase in systolic blood pressure, whereas diastolic blood pressure often stays stable or even declines (Chapter 64). Hypertensive patients age 80 years and older should generally be treated according to current recommendations for people older than 65 years, with a systolic blood pressure goal of less than 120 mm Hg likely associated with lower cardiovascular and all-cause mortality for otherwise healthy older adults.[A1,A2] However, some older adults, especially frail elders, may not tolerate systolic blood pressures this low without side effects, so treatment must be individualized. For some patients over age 80 years, a modest reduction in their multidrug regimen may sustain target blood pressure levels with fewer side effects.[A3] Blood pressure control reduces the incidence of cognitive impairment and dementia (Chapter 371) in older persons with mild cognitive deficits,[A4] and discontinuation of antihypertensive treatment does not improve cognitive, psychological, or general daily functioning.[A5] There is little evidence, however, of the impact of maintaining a lower blood pressure on those who are over age 80 years.

The combination of impaired ventricular filling and the inability to increase the heart rate with stress contributes to the postural hypotension that is seen in 20% of older individuals (Chapter 49), as well as their predisposition to falls and syncope with stresses that younger individuals would tolerate. The reduced ability of the elderly to tolerate cardiovascular stress must be recognized and anticipated whenever they experience a major illness. In addition, coronary artery disease can limit cardiac reserve and increase the risk that hypotension will cause a secondary myocardial infarction.

Hyperlipidemia is common in older adults, and statins are effective in this age group for reducing coronary heart disease events.[A6,A7] However, their favorable cost-effectiveness for primary prevention in persons over age 75 years can be offset by even minor geriatric-specific side effects, and these drugs can be discontinued safely in the setting of advanced, life-limiting illness.[A8] Low-dose aspirin is not beneficial in healthy elderly people because its side effects outweigh its benefits.[A9,A10] However, low-dose edoxaban (15 mg daily) may be a safe and effective option to prevent systemic embolization in elderly patients who otherwise seem not to be safe candidates for anticoagulation.[A11]

All adult cardiac conditions become more common with aging. Exercise training can improve endurance and decrease age-related cardiac stiffness.[A12] Treatment recommendations for specific cardiac abnormalities must balance the potential benefit of targeted interventions against the common multimorbidities seen with aging.[4]

RESPIRATORY SYSTEM

The chest wall stiffens with advancing age, and the lungs lose elastic recoil (Chapter 73).[5] Maximal vital capacity declines by about 40%, but oxygen exchange declines by about 50% because of the additive effect of progressive ventilation-perfusion mismatching (Chapter 73). As a result, the arterial Po_2 of many 80-year-olds is about 70 to 75 mm Hg. The clinical manifestations are often progressive shortness of breath with exercise (Chapter 71) and an increased susceptibility to community-acquired pneumonia (Chapter 85) and even to aspiration pneumonia.

GASTROINTESTINAL SYSTEM

Taste and smell (Chapter 395) decline with advancing age. Food tends to taste less sweet and more bitter.

The esophageal sphincter can become lax (Chapter 124), thereby increasing reflux and even aspiration. Atrophic gastritis reduces the risk of duodenal ulcer but also the absorption of iron (Chapter 145) and vitamin B_{12} (Chapter 150). Delayed gastric emptying can lead to a sense of early satiety and decreased appetite.

A gradual decline in the number of hepatocytes decreases the weight of the liver by about one third by the age of 90 years and decreases the liver's ability to metabolize drugs (Chapter 25). Distal colonic motility from the rectosigmoid to the anal canal declines, and more than 60% of elderly individuals develop constipation (Chapter 122). Diverticula (Chapter 128) become more common with age and are seen in up to 50% of people older than age 80 years.

URINARY SYSTEM

Glomerular filtration declines by about 1% per year, and kidney size declines by about one third in older adults (Chapter 101). Maximal concentrating capacity declines, and it becomes more difficult to excrete a salt load or to conserve water in the face of dehydration.

The bladder becomes more irritable with advancing age and may generate less power, which is especially a problem in men with prostatic hypertrophy (Chapter 114). By comparison, urinary incontinence (Chapter 115) is more prevalent in women. Residual bladder urine volume increases, and nocturia is common. Vaginal and urethral atrophy predispose women to urinary tract infections (Chapter 263).

The kidney is more susceptible to the effects of medications, particularly nonsteroidal anti-inflammatory drugs, which can result in sodium and fluid retention and subsequent hypertension. In elderly individuals, a slight acidemia results from impaired acid excretion and may contribute to the development of osteoporosis.

ENDOCRINE SYSTEM

Growth hormone levels fall with advancing age (Chapter 205), thereby resulting in decreased muscle strength, thinning of bones and skin, and increased central fat. However, growth hormone replacement does not appear to result in improved muscle strength. Levels of thyroid hormones do not decline with age (Chapter 207). Parathyroid hormone levels, however, commonly increase, especially in women, probably in response to the kidney's declining ability to maintain normal serum levels of phosphorus and calcium (Chapters 184 and 227).

The ability of the pancreas to release insulin is blunted with advancing age (Chapter 210), but the kidney's clearance of insulin also decreases. The net result is maintained plasma insulin levels in the fasting state but an increased likelihood of postprandial or stress-induced hyperglycemia. Dramatic declines in estrogen and progesterone production precipitate menopause at an average age of 51 years (Chapter 222). Testosterone levels begin to decrease in men by about 50 years of age, often with resulting declines in sexual function but not in the potency of semen (Chapter 216). Testosterone supplements reverse the muscle loss and sexual implications of declining testosterone levels, but their safety and effect on the risk of cardiovascular complications are uncertain.[6,7]

IMMUNE SYSTEM

Declines in the responsiveness of the immune system explain why the incidence of autoimmune conditions, such as systemic lupus erythematosus (Chapter 245) and multiple sclerosis (Chapter 380), declines in the elderly. However, this same decline explains increased morbidity and mortality with infectious diseases and the increased risk of reactivating infections such as tuberculosis (Chapter 299) and herpes zoster (Chapter 346). These risks emphasize the importance of vaccination against herpes zoster, influenza, pneumococcal pneumonia, and tetanus in the elderly (Chapter 15).

HEMATOPOIETIC SYSTEM

Hematopoiesis (Chapter 142) is generally sustained with aging, except in response to marked stress and inflammatory pathway activation. The one exception is that the hematocrit declines somewhat in older men, presumably owing to their lower testosterone levels. Clonal hematopoiesis, which is the proliferation of a single cell, is more common with aging and increases the risk of cancer, cardiovascular disease, and all-cause mortality.[8]

INTEGUMENTARY SYSTEM

With aging, the epidermis and dermis adhere less tightly and the subcutaneous tissue thins, thereby making the skin feel looser and more likely to wrinkle and ulcerate. Clinical sequelae include senile purpura (Fig. 24-2) as tears in small venules after bumps or abrasions (Chapter 407). Ultraviolet light exposure also predisposes to skin cancer (Chapter 188), rosacea (Chapter 406), xerosis, and hair loss (Chapter 409). Wound healing is also compromised, and complete skin healing can take 5.5 weeks instead of 3.5 weeks in individuals older than age 65 years.

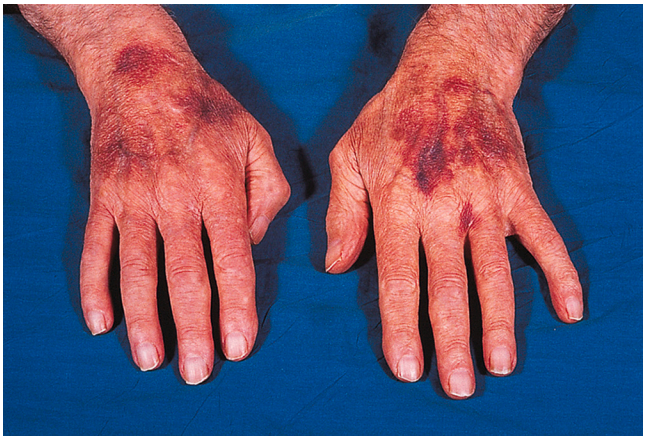

FIGURE 24-2. Senile purpura is a common and benign condition that results from impaired collagen production and capillary fragility in some older adults. In the absence of other signs of disease, no investigation is necessary. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

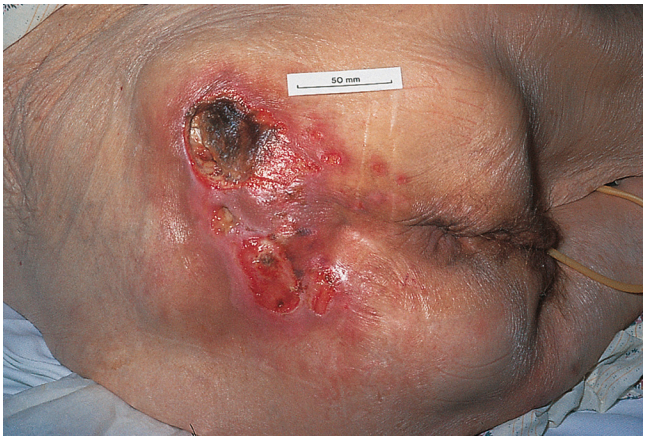

FIGURE 24-3. Severe sacral pressure sore, one of the serious but preventable complications of immobility. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

Pressure Sores

Older adults are more prone to pressure sores when they are bedridden. Pressure sores, which are necrotic areas of muscle, subcutaneous fat, and skin, usually occur between underlying bone and a hard surface (or a soft surface during a prolonged time) as a result of compression and subsequent ischemia (Fig. 24-3). A continuous-pressure threshold of only 30 to 35 mm Hg is needed to cause pressure sores, and a standard mattress can generate pressures five times as high. In addition to pressure injury, other contributing factors include shear injury from rubbing constantly against underlying surfaces, burning injury from friction of the superficial skin layers, and moisture that softens the skin, makes it stick to underlying surfaces, and provides easy access for infection.

TREATMENT AND PREVENTION

Safe positioning, regular turning, avoidance of direct pressure, pressure-reducing beds, and advanced static mattresses or advanced static overlays can reduce the incidence of pressure sores. Alternating air mattresses or overlays are not recommended.[9] Pressure sores should be photographed to establish a baseline. The wound should be freed of any pressure to prevent additional pressure ulcers. Wet-to-dry dressings are a mainstay, and semiocclusive and occlusive dressings also can be helpful. Protein or amino acid supplementation enriched with zinc and antioxidants,[A13] hydrocolloid or foam dressings, and adjunctive electrical stimulation may be useful. Surgical or chemical débridement is often required. Topical or systemic antibiotics (Chapter 261) may be needed. Pressure ulcers usually heal within 6 months, but surgical repair is sometimes required.

MUSCULOSKELETAL SYSTEM

Bone mass and density decrease by about 1% per year but by up to 2 to 3% per year in the first 5 to 10 years after menopause in women (Chapters 222 and 225). In older women with osteopenia, bisphosphonate therapy (e.g., zoledronate, four 5-mg infusions at 18-month intervals)[A14] significantly reduces the risk of nonvertebral or vertebral fractures within 1 year[A15] and therefore is useful in women with a life expectancy longer than 1 year. Tendons and ligaments become less elastic, thereby contributing to a higher incidence of rupture, especially of the Achilles tendon. Sarcopenia is common in older adults.[10] For example, muscle mass declines by about 25% by the age of 70 years and by 30 to 40% by the age of 80 years unless it is offset by exercise.

CLINICAL PHARMACOLOGY

Older adults take a disproportionate share of all prescription (Chapter 25) and nonprescription (Chapter 30) medications, and they are at increased risk of drug-drug interactions. Because older adults have less muscle mass and more fat as a proportion of total body weight, they are more sensitive to the effects of water-soluble drugs and have prolonged effects from lipophilic drugs. Declines in renal and hepatic function reduce the clearance of most drugs, although drugs that are conjugated and glucuronidated are cleared relatively normally. Older people also are more likely to be nonadherent to prescribed regimens owing to the number of medications and their cost, mental impairment, and medication side effects.

SENSORY AND SLEEP

In addition to age-related cognitive decline (Chapters 361 and 361), hearing loss develops in about 25% of individuals older than 65 years (Chapter 396), with decreased neural transmission leading to difficulty in discriminating important sounds from background noise. Presbycusis diminishes the ability to hear high-frequency sounds.

The thickening and stiffening of the lens diminish the ability to focus on nearby objects and increase glare (Chapter 391). Transmission of light through the lens may decline by 50% or more, so elderly individuals require more ambient light. Vitreal detachment causes floaters that also can interfere with vision. Decreased tear production causes dryness of the eyes. All of these conditions contribute to a decline in visual acuity to the extent that 40% of men and 60% of women older than 65 years have a visual acuity of 20/70 or worse.

Older adults tend to have difficulty in sleeping (Chapter 374) yet spend more time in bed. Sleep apnea also becomes more common with advancing age (Chapter 374).

FRAILTY

EPIDEMIOLOGY

Frailty in older adults is a geriatric syndrome of weakness, slowness, and weight loss, owing to an aggregate of comorbid conditions. Frailty serves as a clinical indicator of which older adults are at high risk for adverse outcomes, including delirium (Chapter 361), falls, and mortality.[11,12] Measures of frailty are also increasingly utilized to identify older adults who are at highest risk for adverse health outcomes related to procedures or medical treatments, including intensive care,[13] general surgery,[14] hip fracture surgery,[15] or coronavirus disease 2019 (COVID-19) infection.[16]

PATHOBIOLOGY

The biology that differentiates vulnerable or frail older adults from resilient or robust older adults is complex and multisystemic in nature. For example, diminished heart rate variability, which is a marker of dysregulated sympathetic nervous system activity, is associated with aging, frailty, and cardiac arrhythmias. Frail older adults have significantly higher levels of salivary cortisol during the afternoon nadir period, thereby suggesting chronically increased activity of the hypothalamic-pituitary-adrenal axis. Elevated levels of inflammatory cytokines, especially IL-6, tumor necrosis factor-α receptor 1 (TNFR1), and C-reactive protein, are strongly related to functional decline, frailty, chronic disease, and mortality in older adults, probably owing to increased fat, more senescent cells, and free radical production from altered mitochondria. IL-6 is likely to have a negative impact on stem cells and satellite cells, which in turn may contribute to the chronic anemia and age-related declines in skeletal muscle (sarcopenia) and bone mass (osteopenia) commonly observed in frail, older adults. TNFR1 stimulates apoptosis and necroptosis, which are cell programs that lead to cell death and possibly tissue depletion and vulnerability later in life. In addition to stress response systems, endocrine factors that normally maintain muscle mass play a role in frailty. For example, the adrenal androgen dehydroepiandrosterone sulfate and insulin-like growth

factor 1 are significantly lower in frail adults. Future preventive or treatment strategies to reduce frailty and improve resiliency may target some of these stress responses or endocrinologic changes.

CLINICAL MANIFESTATION AND DIAGNOSIS

Validated frailty screening tools (Table 24-1) enable physicians to identify patients at highest risk of side effects, adverse outcomes, and mortality and to develop preventive interventions that will decrease risk and improve quality of life. One approach is to measure physiologic parameters such as grip strength, walking speed, and weight loss, as well as to gather information about activity and fatigue levels. With use of this approach, the prevalence of frailty rises with increasing age; approximately 10% of community-dwelling adults older than 65 years meet these frailty criteria and subsequently are at increased risk of functional decline, falling, hospitalization, and death, even after adjustment for age, socioeconomic and smoking status, and multiple common disease states.

TREATMENT AND PREVENTION

Interventions should be targeted to the specific characteristics of a patient's frailty. Increasing physical exercise is the mainstay of most programs.[A16] Focused prevention of iatrogenic injuries or recurrent hospitalizations and remediation of symptoms are often warranted for frail vulnerable older adults (Fig. 24-4). Physical activity, exercise interventions, and nutritional supplementation can reduce disability and symptoms and improve quality of life across the spectrum of robust to frail older adults. In addition, exercise and weight loss together improve function in obese and frail older adults. Other options include a team-based approach that engages the patient, family members, caregivers, health care providers, and social workers. Classic palliative care (Chapter 3), with appropriate pain management, less invasive treatment plans, limited hospital visits, and organized home care plans, can greatly improve quality of life. If the patient has frequently been admitted to an inpatient setting, a program for all-inclusive care or a medical daycare setting may help prevent recurrent admissions and improve quality of life. Once admitted to the hospital, frail older adults may benefit from being congregated in a unit that specializes in their needs and can provide attention to their functionality, continence, sleep disturbances, delirium, and palliative care issues.

TABLE 24-1 FOUR COMMONLY USED INSTRUMENTS TO MEASURE FRAILTY IN OLDER ADULTS, WITH RELEVANT MEASUREMENT DOMAINS AND SCORING CRITERIA

INSTRUMENT	DOMAINS	SCORING
Physical frailty (biologic syndrome model)*	Physical function (slowness, low activity, weakness), nutritive (weight loss), and exhaustion	Score range: 0-5 Frail = ≥3 criteria present Intermediate/pre-frail = 1-2 criteria present Robust = 0 criteria present
Cumulative Deficit Frailty Model (comorbidity model)†	Diseases, ability in ADL, health attitudes/values, and symptoms/signs from the clinical and neurologic examinations	Number of deficits present and divided by the number of deficits taken into consideration Higher proportion equates to a higher level of frailty
Vulnerable Elders Survey (VES-13)‡	Physical function and ADL/IADL disability	Score range: 0-10 Frail = score ≥3
1994 Frailty measure (functional domains model)§	Physical function, nutritive function, cognitive function, sensory problems	Subject scoring a 3 or higher on at least one item in any domain is considered to have a problem or difficulty in that domain Frail = problems/difficulties in ≥2 domains

*Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156.

†Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007;62:738-743.

‡Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc*. 2001;49:1691-1699.

§Strawbridge WJ, Shema SJ, Balfour JL, et al. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci*. 1998;53:S9-S16.

Details on the use and implementation of these tools can be found in the referenced articles.
ADL = activities of daily living; IADL = instrumental activities of daily living.

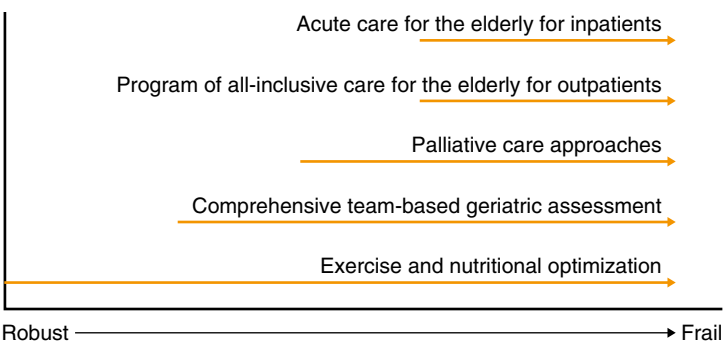

FIGURE 24-4. Assessment and treatments in frail and vulnerable older adults.

PROGNOSIS

Frailty increases the likelihood for development of influenza or influenza-like illness in the 6 months after vaccination; the likelihood of requiring care in a skilled nursing or long-term care facility after hospitalization for general surgery; the likelihood of poor outcomes in patients with cardiovascular disease; poor renal transplant graft function and early hospital readmission after transplantation; falls, hospitalization, and mortality in patients on hemodialysis for chronic renal failure; and the risk of death in aging intravenous drug users. Biologic differences between frail and non-frail older adults (see Fig. 24-1) drive the marked vulnerability to adverse outcomes observed in the frail subjects.

FALLS

Falls are a common manifestation of frailty. Contributing factors include cardiopulmonary disease, poor eyesight, hearing loss, balance disturbances, weakness, movement disorders, neuropathies, poor judgment, depression, osteoporosis, arthritis, and foot disorders.[17] The risk of falling also increases in patients who take more prescription medications, especially hypnotics, muscle relaxants, antihypertensive agents, diuretics, and antidepressant medications. Environmental risks include stairs, loose objects, rugs, poor lighting, poorly fitting shoes, uneven pavements, and slippery surfaces.

Patients who have fallen or have a fear of falling should have a falls assessment, including measuring orthostatic blood pressure, assessing vision, reviewing medications, and testing balance, gait, and lower extremity strength.[18,19] Exercise alone and exercise combined with other interventions (e.g., vision assessment and treatment; environmental modification) lower the risk compared with usual care,[A17–A19] but intensive, nurse-led, individualized plans may not provide incremental benefit over good baseline care.[A20,A21] Data on vitamin D supplementation to reduce falls have been inconclusive, but recent trials indicate no benefit.[A22,A23]

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For the General References and other additional features, please visit Elsevier eBooks+ at https://ebooksmedicine.elsevier.com.

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GOLDMAN-CECIL MEDICINE

27TH EDITION

Volume 1

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Elsevier
1600 John F. Kennedy Blvd.
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Philadelphia, PA 19103-2899

GOLDMAN-CECIL MEDICINE, TWENTY-SEVENTH EDITION
ISBN: 978-0-323-93038-3
Volume 1 ISBN: 978-0-323-93034-5
Volume 2 ISBN: 978-0-323-93035-2

INTERNATIONAL EDITION
ISBN: 978-0-323-93039-0
IE Volume 1 ISBN: 978-0-323-93036-9
IE Volume 2 ISBN: 978-0-323-93037-6

Publishing Director, Medical Reference Content: Dolores Meloni
Senior Content Development Manager: Laura Schmidt
Publishing Services Manager: Catherine Jackson
Senior Project Manager: Daniel Fitzgerald
Designer: Maggie Reid

Printed in Poland

Last digit is the print number: 9 8 7 6 5 4 3 2 1