

Dosage Adjustments Related to Young or Old Age and Organ Impairment

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Abstract

Differences in physiology related to young or old age and/or organ system impairment alter the absorption, distribution, metabolism, and excretion of many medications and consequently their effectiveness and toxicity. This module discusses common alterations in medication use and dosage that are required in the pediatric age group, in the elderly, and in patients with renal or hepatic disease.

Keywords

entrustable professional activities (EPA) in clinical pharmacology, medical education, prescribing practices, drug interactions, medical misadventures

Medications are administered in a variety of ways: orally, intravenously, intramuscularly, subcutaneously, transdermally, by inhalation, by elution from implants, and through the ocular, nasal, otic, rectal, and vaginal mucosa. Most are absorbed from the site of administration into the bloodstream and distributed to their site of action (and to other tissues, which may result in toxicity or unintended effects). They are often metabolized to active and inactive metabolites by the liver and other organs. Finally, they are excreted, primarily by the kidneys but also in the bile, through the skin, and by exhalation.

Differences in physiology related to young or old age and/or organ system impairment can and do alter every step in this sequence, consequentially altering the effectiveness and toxicity of almost any drug. This review discusses common alterations in medication use and dosage that are required in the pediatric age group, in the elderly, and in patients with renal or hepatic disease because of physiologic differences in those groups relative to adults who are healthy or have limited medical problems. In the pediatric age group most of the differences are due to a lack of full maturation of physiologic functions. In the elderly and those with renal or hepatic disease, the differences are related to diminished or diseased organ function. These differences are sufficiently profound as to require individualized adjustment of medication doses in many cases and avoidance of certain medications altogether in some cases in these groups of patients. Clinical vignettes are provided in the appendix to illustrate the application of the principles described in this module.

Pediatric Dosage Adjustment

Drug therapy in pediatrics focuses on designing and prescribing optimal dose regimens to treat or cure

disease in children across the age continuum, ie, infants born after as little as 22 weeks of gestation (normal 38 to 40 weeks) to young adults who are 18 years of age. In some situations, particularly those patients with a chronic disease originating during childhood or on a genetic basis, eg, congenital heart disease or cystic fibrosis, patients may be cared for by their pediatric care givers until they reach 21 to 25 years of age. This physiologic maturation provides a unique challenge to pediatric care providers with respect to the optimal use of drug therapies in addition to factors shared by adult care providers that must also be considered, such as disease state, organ function, genetic influences, use of interventions such as dialysis, and many others.

Age is a primary influence on drug disposition. Substantial changes in organ function and enzyme processes that occur before and after birth through completion of puberty have major influences on drug disposition.^{1,2} Because age and body size are usually highly correlated, including organ size and functional capacity, age is a strong indicator of drug disposition.³

The time course and magnitude of growth and development of physiologic functions drive the design of optimal pharmacotherapy and the patient's response

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to these regimens. The many influences growth and development have on drug disposition and effect are far greater in the pediatric patient than in any other patient population. Following birth, through infancy, childhood, and up to puberty, body size and major organ function are continually changing. Renal and liver function, the major organs involved in drug elimination (clearance), change with age.^{4,5} Specific time lines for organ functional development and maturation are well known, but growth and disease can substantially alter the normal progression. Because age, body size, and organ function are normally closely related, drug dosing in the pediatric patient is often linked to a child's body weight (ie, drug dose = mg drug/kg patient body weight). Drug dosing as a function of body weight attempts to "control" for these ontogenic changes³ but, above all, is simple to institute in the office or at the bedside. It is important for the clinician to keep abreast of the pediatric patient's growth so that the patient receiving chronic drug therapy does not outgrow his or her dose and experience a recrudescence of the symptoms or worsening of the disease. Alternatively, sick infants and young children may experience failure to thrive or growth retardation in which body weight and age, when plotted on age-linked growth charts, are abnormal, and the weight-based drug dose may be too much and need to be reduced.

Once a child's weight-based dosing results in drug doses equal to adult doses (eg, around puberty), the "usual" or maximum adult dose is often prescribed with acceptable tolerability and benefit. Although an individual dose may equal the adult dose, the drug dose may need to be administered more frequently to compensate for more rapid body clearance observed in infants and children, ~1.5 years to puberty, when clearance is expressed in terms of liters per hour per kilogram. There are other methods to scale clearance rather than by simple body weight, such as by body surface area or allometric scaling (an exponential function of body weight). These scaling methods result in a more intuitive steady increase in clearance from approximately age 2 years as the child matures into adulthood.⁶ However, these scaling methods, which require drug doses to be equally scaled to body surface area or an exponential function of weight, are not commonly used in routine clinical practice because of their increased complexity.

The amount and distribution of body water (intracellular + extracellular = total body water [TBW]) also develop with age.⁷ Important to optimal pediatric pharmacotherapy is the fact that the more premature the infant the greater is its TBW content. For example, a 27-week-gestation premature infant may have 80% TBW vs the normal 60% for an adult. Thus, to account for this increase in drug volume of distribution (V_d), the

individual dose for the premature infant on a milligram-per-kilogram basis is often much higher than that administered to older children and adults. Growth and development are "moving targets" in pediatric practice, and the physician needs to be precise in the dose calculation to accommodate these natural processes while he or she concurrently monitors the patient for the desired effect(s) and lack of associated drug-induced adverse effect(s).

Included in the appendix are 2 cases that are illustrative of common, important clinical pharmacology challenges faced by the pediatric practitioner and several references for further reading.

Geriatric Dosage Adjustment

Individuals aged 65 and older are in the geriatric age group. Geriatricians often think of the elderly as falling into 3 categories, the "young old" aged 65 to 74, the "old old" aged 75 to 84, and the "frail elderly" aged 85 and above. More than half of the elderly have 3 or more chronic medical conditions, with the number of conditions rising with age, and they commonly take from 4 to 9 or more medications and over-the-counter products including herbal products and dietary supplements daily.⁸ Managing patients with multiple chronic conditions requires careful and judicious balancing of the risks, benefits, and costs of available therapies. It is frequently necessary to forgo optimal treatment for 1 condition in order to avoid worsening another or inducing serious drug interactions and side effects. Identifying and supporting patient preferences, preserving quality of life, and being cognizant of individuals' prognoses are important in all patients, but especially in the elderly and other groups with limited life expectancy.⁹ The physician should by no means withhold effective treatments because a patient is aged, but it is very important to be cognizant of the burdens of treatment in the elderly and to modulate pharmacotherapy accordingly.

There are a number of age-associated changes in pharmacokinetics and pharmacodynamics that must be kept in mind in designing pharmacotherapy for the elderly.^{8,9} There are an age-related increase in the body fat/water ratio and a decrease in plasma protein that result in alterations in drug distribution: fat-soluble drugs have an increased volume of distribution (and potentially diminished effectiveness), whereas highly protein-bound drugs may have a greater free (active) concentration. Such changes in distribution may be exacerbated by conditions that increase body water such as ascites. These changes may but do not necessarily alter drug effectiveness and must be assessed on a case-by-case basis. Decreases in liver mass and blood flow and in the activity of certain drug-metabolizing

enzymes result in decreased clearance of many drugs, so that reduction of doses may be necessary. Smoking, alcohol, caffeine, and concomitant medications may also affect drug metabolism. The age-related reduction in glomerular filtration rate in the elderly slows the elimination of many drugs and may require a reduction in drug doses; this will be exacerbated in the presence of acute or chronic kidney disease.^{9,10} Reduction of creatinine clearance below 50 mL/min is common in the elderly and sufficient to require dosage reduction of some medications. Reduction of creatinine clearance below 30 mL/min requires reduction of the doses of many drugs or even their avoidance altogether. Intrinsic changes associated with aging in cardiac pacemaker cells and conduction systems make the elderly more susceptible to drug-induced cardiac conduction disorders including prolonged QT intervals, bradycardia, tachyarrhythmias, and Torsades de Pointes.¹¹

Because the elderly so commonly take multiple medications and supplements, drug-drug and drug-food interactions are common.¹⁰ A number of minerals (zinc, iron, aluminum, calcium, and magnesium) can reduce oral absorption of certain drugs. Vitamin K-containing supplements can reduce warfarin's effect. Medications may alter the taste of food (dysgeusia) or decrease saliva production (xerostomia), reducing appetite and making swallowing more difficult. A drug's effect can be altered by concomitant use of another medication by several mechanisms including displacement from protein-binding sites, inhibition or induction of metabolic enzymes, or because the 2 drugs have either similar or antagonistic pharmacologic effects. Careful monitoring of therapeutic and toxic effects of drugs and individualization of treatment accordingly are essential to successful pharmacotherapy in the elderly.

Included in the appendix are 3 geriatric clinical pharmacology vignettes and several references for further reading.

Organ System Impairment Dosage Adjustment

The liver and kidney play important roles in the absorption, distribution, metabolism, and elimination of most drugs. Disease (chronic or acute) of the liver and kidney can have an impact on each of these phases of drug disposition.^{12,13} Drug clearance is comprised of nonrenal mechanisms (metabolism, biliary excretion, and transport) and renal excretion of parent drug and metabolites. Liver and kidney disease may lead to altered pharmacokinetics (PK), systemic exposure, and response (efficacy or toxicity) and may warrant a dose adjustment.^{12,14}

Both acute and chronic liver disease can have a major impact on the PK of multiple drugs used in medical practice. The liver is involved in the clearance of many drugs through metabolism and biliary excretion. The effect of chronic liver disease (e.g. hepatitis, cirrhosis, and cholestasis) on the PK of drugs is commonly studied during drug development and dose adjustment recommendations are typically made based on these data.¹⁵ In addition, drug-induced acute liver disease is caused by certain drugs and can result in profound adverse events.

Chronic kidney disease (CKD) has been shown to affect all components of drug disposition. CKD can decrease the elimination of drugs primarily eliminated by the kidney, resulting in decreased drug clearance and a resultant higher exposure potentially leading to adverse reactions.^{13,14,16} The effect of CKD on drug disposition is a major area of research focused on increasing our understanding about providing optimal dosing in CKD patients.

Drug-induced acute kidney injury (AKI) resulting in nephrotoxicity is a relatively common and often debilitating complication of numerous drugs. It has been implicated in up to 20% of hospital admissions for AKI and as many as 60% of in-hospital cases of AKI.¹⁷ The kidneys receive 25% of the cardiac output, resulting in increased exposure to drugs in the systemic circulation and thus increased susceptibility to nephrotoxic injury compared to many other organs.¹⁸ In addition, glomerular ultrafiltrate is progressively concentrated as it travels along the nephron; it is concentrated >3-fold in the proximal tubule and >100-fold in the distal tubule and collecting duct.¹⁹ Consequently, the renal tubules and interstitium are exposed to extremely high concentrations of drugs undergoing glomerular filtration and are particularly susceptible to toxicity. As a result, clinicians must be cognizant of the potential drug toxicity profile and the specific patient risk factors that increase renal vulnerability to nephrotoxicity.²⁰

Early detection of nephrotoxicity is of utmost importance in order to discontinue the offending agent, initiate supportive therapy, and thereby minimize renal damage. The most common manifestation of nephrotoxicity is a decline in GFR leading to a rise in serum creatinine and blood urea nitrogen (BUN). Serum creatinine and BUN are used as surrogates of kidney function, not as measures of injury per se, and typically significant kidney injury must have occurred before a rise in either is observed; unfortunately, they are relatively insensitive markers of kidney injury.²¹

The case vignettes described in the appendix illustrate the clinical impact of both acute and chronic liver and kidney disease on the PK and toxicity of commonly used drugs. Several references are provided for further reading.

Appendix: Clinical Vignettes

Pediatric Vignettes

Clinical Vignette: Apnea of Prematurity. Sammy is now a 7-week-old 3.4-kg former 30-week prematurely born male with a history of 2 previous hospital admissions for apneic episodes. He is brought to the emergency department (ED) by ambulance from his home following an ~30- to 45-second apneic event where his mother described him to be “blue and stiff,” which resolved upon stimulation. He has an apnea monitor at home and is prescribed oral caffeine citrate 10 mg (0.5 mL) once daily. His past medical history is significant for premature birth, sepsis, and a pulmonary disease of unknown etiology with apnea episodes lasting from 20 to 30 seconds, although 1 was witnessed to last as long as 2 minutes. Apnea of prematurity (AoP) is a developmental disorder of breathing that occurs in prematurely born infants, usually before 34 weeks of gestation, and lasts until the infant achieves full-term gestational age (38 to 40 weeks of gestation). For infants born after <28 weeks of gestation, this disorder can last far beyond the time of term gestation. AoP is characterized by a cessation of breathing for more than 20 seconds or for >15 seconds when coincident with bradycardia and/or cyanosis.²²

The goal of AoP treatment is to minimize or prevent apneic episodes, minimize/prevent lung disease during intubation, and prevent the need for reintubation of the recently extubated infant. For Sammy, the goal is clearly to minimize or prevent apneic episodes until they no longer occur.

On day of life 2 (DOL2) his apnea of prematurity was treated with an intravenous (IV) caffeine citrate 20 mg/kg loading dose followed by a maintenance dose of 5 mg/kg caffeine citrate IV once daily to achieve and maintain the desired target serum caffeine concentration between 15 and 20 mg/L. This dosing and resultant serum caffeine concentrations achieved near elimination of his apneic episodes, and Sammy was discharged home at age 3 weeks to receive orally administered caffeine citrate.

One month later in the ED, Sammy was described as an appropriately developed and nourished infant in mild distress with no significant abnormalities in his vital signs or physical exam; specifically, his head, eyes, ears, nose, and throat appeared normal, his neck was supple, and tympanic membranes were clear; heart exam revealed a regular rate and rhythm without murmur, brisk capillary refill; lungs were clear to auscultation bilaterally; his abdomen was nontender without distention with positive bowel sounds, and his skin was normal in appearance. He was breathing normally on room air (pulse oxygenation >98%). Home medications included simethicone 20 mg q12h, albuterol

aerosols as needed, and caffeine citrate solution 10 mg (0.5 mL) administered orally once daily. Blood was obtained for routine laboratory analysis including a serum caffeine concentration that was reported as 3.7 mg/L. Again, the desired target concentration for Sammy is 15 to 20 mg/L. His oral caffeine citrate dose was increased to 20 mg (1 mL) to match his increase in body weight due to normal growth, and he was sent home to consult with his healthcare provider and determine if the new caffeine dose is correct and to determine how much longer Sammy will require caffeine therapy.

Commentary. Sammy is now a 37-week gestational-age infant with AoP. He was relatively well controlled following birth and at the time of his hospital discharge home. On discharge he was prescribed oral caffeine citrate to treat his apneic episodes until he “grew out of them.” However, in the past few weeks he has experienced a few short apneic episodes with the latest on the day of this admission, when his mother described him to be “stiff and blue” for a brief time period. The course of Sammy’s disease resolution/recurrence is a case study in developmental clinical pharmacology. First, his caffeine dose was not increased coincident with his normal growth. Second, maturation of organs responsible for caffeine metabolism and excretion occurs rapidly during the time period associated with the last trimester.

Caffeine is the drug of choice for AoP.²³ A methylxanthine (similar to theophylline and aminophylline), caffeine inhibits the activity of 2 of the known 4 adenosine receptors, leading to relaxation of smooth muscle, central nervous system (CNS) and cardiac stimulation, and diuresis. In AoP, caffeine stimulates the respiratory center in the brain and may decrease the CNS threshold to carbon dioxide, increase the CNS response to hypercapnia, decrease diaphragmatic fatigue, and may have an anti-inflammatory effect on the maturing lung, an extremely important and often understated effect.

Important to drug dosing in any patient is the function of organs and/or processes involved in drug elimination (body clearance). Young infants and children are often described as having “poor renal function” and/or “poor liver function.” On a functional basis and when compared to adult values this is true; however, this function is “normal” for the individual’s age. On average, renal function is extremely limited and highly variable during the neonatal period. Nephrogenesis is usually complete by approximately 33 to 35 weeks of gestation, although function is highly variable, maturing to achieve adult capacity for glomerular filtration and secretion at approximately 1+ years of age.²⁴ Glomerular and tubular functions mature at differing

rates, with glomerular and tubule sizes continuing to grow larger through childhood, which may partially serve as the basis for the observed increase in weight-normalized drug clearance for many drugs, compared with adult values, that can persist for children at ~2 years of age until puberty, when pediatric and adult values in drug clearance begin to equalize. This maturational time frame can be shorter or longer for infants born at full term and will be longer for infants, as in Sammy's case, born prematurely.

Full renal function development for very low-birth-weight (VLBW) infants and premature infants can continue up to 8 years of life, lagging behind functional capacity observed in full-term infants' development.^{4,24} To account for the maturational changes occurring at critical gestational age time points, clinicians often base their drug prescribing for infants on their postconceptional age (PCA). PCA is simply the gestational age plus the postnatal age, usually in weeks, and is a simple means of "correcting" prematurely born infants' age with anticipated organ maturity and even body weight and growth. On admission, our patient was 37 weeks PCA.

The liver is the organ primarily responsible for drug metabolism. Hydrophilic compounds are often easily eliminated in urine without modification, whereas lipophilic compounds require some form of alteration/metabolism to form a more water-soluble compound/metabolite(s), fostering renal elimination. Some drugs are eliminated from the body via the bile. Liver function maturation is dependent on PCA, increasing with age. Drug metabolism by the liver is usually divided into 2 phases, phase I (oxidation, reduction) and phase II (conjugation, synthetic) functions that mature at different rates dependent on gestational and postnatal ages, disease, genomics, and much more.^{1,2,5,25} The primary phase I drug-metabolizing enzymes (DMEs) include the cytochrome P450 (CYP) superfamily (eg, CYP1A2, CYP2D6, CYP3A4/5) and phase II enzymes (eg, UDP-glucuronosyltransferases [UGT], N-acetyltransferases [NAT], sulfotransferases [SULT]). Phase I and phase II DMEs display a unique developmental pattern with substantial inter- and inpatient variability.^{1,2} For simplicity in linking developmental maturation of functional activity for many of these isoenzymes, select DMEs have been categorized into 1 of 3 groups: group 1 are those enzymes expressed at their highest level during fetal life that disappear over the infant's first 2 years of life (eg, CYP3A7, SULT1A3/4); group 2 comprises enzymes with a modest amount of activity at birth with increasing activity later in life (eg, CYP2C19, CYP3A5, SULT1A1); and group 3 enzymes with modest ontogeny during the second and third trimesters of pregnancy and have important increases in activity throughout infancy

and some into childhood (eg, CYP1A2, CYP2C9, CYP2D6, CYP3A4).

Important to this case, the metabolism of caffeine, which is primarily a CYP1A2 substrate, is highly variable at birth, reaching adult values by 3 years to possibly as much as 9 years of age.²⁶ For the first month of life (PCA ~42 weeks in full-term infants) caffeine is primarily eliminated from the body renally, which also explains why dosing can be once daily. Sammy's estimated caffeine elimination half-life ($t_{1/2}$) is 70 to 100 hours, easily accommodating once-daily dosing, and is a direct result of his age-related "decreased" renal function observed in infants of his PCA. In contrast, in older children and adults, where the body elimination of caffeine is dependent on liver function and primarily CYP1A2 activity, the caffeine $t_{1/2}$ usually averages ~5 hours.

Important but beyond the scope of this minireview are the maturational patterns observed in cell transporters, which are membrane-bound proteins that facilitate the movement of substrates across membranes, ie, efflux or influx pumps that enhance the cellular extrusion or uptake of many substrates including drugs. The most important to drug absorption, distribution, and elimination would include P-glycoprotein (P-Gp/MDR1) and others modulating drug transport in the gastrointestinal tract, liver, kidney, placenta, and blood-brain barrier, to note a few.²⁷

Clinical Vignette: Vancomycin Toxicity in Children. An 8-year-old boy who was generally healthy was admitted with signs and symptoms of acute bacterial pneumonia. He was started on ampicillin intravenously and azithromycin orally, but he deteriorated over the first 24 hours of admission. His initial blood culture revealed Gram-positive cocci in clusters, and his physician stopped azithromycin and changed the ampicillin to vancomycin because of concern for methicillin-resistant *S aureus* (MRSA). Although the FDA-approved dose in this age range is 40 mg/kg per day divided every 6 hours, his physician decided to follow the guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of community-acquired pneumonia.²⁸ The guidelines recommend a range of 40 to 60 mg/kg per day, and thus the child was started on 15 mg/kg per dose intravenously (IV) every 6 hours (60 mg/kg per day).

According to additional IDSA guidelines, the appropriate blood concentration of vancomycin for this infection in adults is a trough concentration of 15 to 20 mg/L obtained just before the fourth dose.²⁹ There are no similar recommendations for children, but as the pathogenesis of acute bacterial pneumonia is similar in children and adults, the physician decided to use the same target. Accordingly, the first measured

vancomycin trough concentration before the fourth dose at the end of day 1 of therapy (hospital day 2) was 10 mg/L. This was far below the desired target, so the physician increased the dose by 50% to 90 mg/kg, expecting the trough to increase by approximately the same amount to 15 mg/L because vancomycin displays dose-proportional (“linear”) pharmacokinetics. Prior to the fourth new dose on hospital day 3, the new trough concentration was 17 mg/L. The bacterial isolate from the blood on hospital admission was confirmed to be MRSA with a vancomycin minimum inhibitory concentration (MIC) of 1 mg/L.

Over the first 72 hours, the boy required several IV normal saline boluses and IV fluids to maintain proper blood pressures. His urine output was a little below normal, and his daily weights were rising as he accumulated fluid. Because of the boy’s unstable condition and the physician’s discomfort with such a high vancomycin dose and the associated risk of nephrotoxicity, the physician continued to monitor renal function with frequent serum creatinine measurements. Unfortunately, on the fifth hospital day, the patient’s serum creatinine increased from a baseline of 0.6 mg/dL to 2.8 mg/dL. A stat trough vancomycin concentration was 45 mg/L. The boy’s creatinine clearance was estimated to be only 15 mL/(min·1.73 m²), and the drug was suspended. Vancomycin concentrations thereafter were measured daily until the concentration fell to 12 mg/L, which was the first value below the low end of the target range. At this point a single dose of 10 mg/kg was given. Twenty-four hours later the concentration was 9 mg/L. By 1 week into his hospitalization he was on a vancomycin regimen of 15 mg/kg per dose once daily, guided by daily trough concentrations. His blood culture remained positive for 2 days and then sterilized. He was eventually diagnosed with an MRSA pneumonia complicated by empyema that required surgical drainage. Therefore, he required vancomycin for a total of 4 weeks. By the second week, his serum creatinine had begun to improve, and thus his dose was gradually increased again to 60 mg/kg per day, at which point his trough concentration remained stable at about 12 to 15 mg/L. He completed his therapy without further incident, and he was discharged home without residual complications.

Commentary. This case illustrates several points about the use of a drug and dosing individualized to a specific patient by measuring drug concentrations. Although this case study is for a child, these points are generalizable to patients of all ages.

Although a drug’s Food and Drug Administration (FDA) package insert contains all approved dosing information, physicians and pediatricians in particular are often forced to administer drugs to patients who are

not included in the population described in the package insert. Even when approved dosing recommendations exist, dosing must always be guided by a careful assessment of the benefits and risks to the individual patient and thoughtful consideration of the dose to use, which may include use of available published data/guidelines. Further, there should be a frank discussion with the patient or the patient’s legal representative(s) about the decision process to select not only the medication but also the dosing regimen. Here, the physician decided to start with a higher dose than the FDA-approved one, but a dose that was nonetheless supported by guidelines and, in the judgment of the physician, warranted due to the age and condition of the patient. The use of a drug in the manner described is often referred to as “off-label” prescribing, ie, prescribing a drug and/or drug dose in a manner not included in the approved FDA labeling. This is legal and common, although physicians should be well aware when they are using a drug off label because the risks to the patient may be increased.

Once the drug is started, and especially when the dose or the patient is unusual, close patient monitoring and follow-up are critical. A responsible physician will carefully assess for both efficacy and toxicity associated with the drug. For some drugs, such as vancomycin, concentration targets in specific biologic fluids have been largely (but not universally) agreed upon. These “therapeutic” targets serve as surrogate endpoints that can be more quickly measured than the truly desired clinical endpoint, which in this patient was resolution of the pneumonia, empyema, and bacteremia. Whether drug concentration monitoring is employed or not, the physician must be prepared to adjust the dose or even change the drug if suboptimal efficacy or mounting toxicity is detected. Of course, the use of drug concentrations to guide dose adjustments will give confidence to any such changes. For this boy, his initial low vancomycin serum concentration in the face of a high dose was most likely due to increased volume of distribution associated with sepsis, fluid resuscitation, and “third spacing” of intravascular fluid into the extravascular tissue. As his sepsis resolved and his volume of distribution normalized, his very high vancomycin dose unfortunately caused increasingly high serum concentrations that injured his kidneys, further increasing vancomycin concentrations because the drug is eliminated from the body almost completely via the urine. This scenario plays out all too often in septic patients who are treated with vancomycin.

The strategy of monitoring serum vancomycin concentrations and adjusting doses presented in this case study is the typical one used in most clinical settings. Although it is better than no monitoring at all, it is very reactive and not proactive. Because the target serum vancomycin trough range of 15 to 20 mg/L for severe

invasive infections is a steady-state range, the measured trough must also be under steady-state conditions. This is true for most drugs that are monitored with blood concentrations. However, clearly this patient was not in a stable condition and was unlikely to be at steady state. Furthermore, even if he were stable, 97% of steady state is only achieved after 5 half-lives of the drug. So this strategy can result in unnecessary and cumbersome delays in dose adjustment. Furthermore, intuitive dose adjustments by guesswork are the least precise method. A better approach is to use clinical pharmacology to estimate pharmacokinetic parameter values, such as volume of distribution, elimination, or clearance, from measured concentrations. Once these parameters are estimated, concentrations arising from doses can be predicted and controlled with much better precision and accuracy. This type of analysis takes training that can be accomplished by a motivated physician or pharmacist. It can be as simple as basic pharmacokinetic equations or as sophisticated as a Bayesian approach using a population model of drug behavior combined with specific information from the individual patient. Estimation of pharmacokinetic parameters by the use of basic equations is straightforward, but it usually requires multiple blood samples and rigorous timing. Estimation by Bayesian analysis is complex and requires the use of software tools, but it is the most accurate and precise way to manage a patient with the fewest number of blood samples.^{30,31} In all cases, physicians should not use drugs as sledgehammers, with an attempt to make 1 universal dose fit all patients. Rather, they should learn to use drugs as scalpels, with finesse and dexterity, using sound principles of clinical pharmacology that are either learned or “borrowed” from appropriately trained colleagues.

Geriatric Vignettes

Clinical Vignette: Delirium/Dementia. An 83-year-old woman living largely self-sufficiently in the assisted living wing of a comprehensive elder-care facility was found to be uncharacteristically unkempt and slightly confused by the nurse's aide on her routine morning rounds. On examination, the patient had a mild tachycardia, normal blood pressure, and low-grade fever. She was transferred by ambulance to the local hospital Emergency Room. Examination there confirmed normal blood pressure, mild tachycardia, low-grade fever, and orientation $\times 2$ (the patient was uncertain of the date/day of the week). Laboratory testing revealed bacteriuria and a mild leukocytosis. Urine cultures were initiated. The patient was admitted and placed on broad-spectrum antibiotics for a presumed urinary tract infection. Later that evening she was found by the nurse to be agitated and confused (unaware of the date or her location). The medical resident on call

examined the patient briefly and prescribed diazepam for agitation.

The following day urine culture results confirmed an acute urinary tract infection. By that time the patient was completely disoriented, agitated, and confused and had to be restrained and sedated. She was mistakenly assumed to have dementia. Chlorpromazine for agitation was included in the discharge orders but fortunately not administered before she was discharged to the nursing home at her comprehensive elder-care facility to complete a course of antibiotics for the urinary tract infection. Fortunately an astute geriatrician examined her on admission to the nursing home and immediately discontinued diazepam and chlorpromazine. The patient recovered quickly from her urinary tract infection and very slowly from her delirium but eventually was transferred back to her home in the assisted living wing of the facility, where she gleefully told all her friends and family about the incompetence of the medical resident who had prescribed not 1 but 2 drugs that are almost always inappropriate in the elderly.¹⁰

Commentary. Elderly persons tend to have reduced immunocompetency, and an acute pulmonary or urinary tract infection or even sepsis may be manifested by lethargy and confusion rather than high fever and marked leukocytosis. When a previously well-compensated elderly person suddenly becomes confused, look for an infectious cause.

Elderly persons who are functioning well in a familiar setting may become confused and agitated when abruptly transferred to an unfamiliar and even alien environment such as a hospital, particularly when acutely ill. Confusion may be especially apparent when the patient is fatigued late in the day, a phenomenon familiarly known as “sundowning.”

Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents such as diazepam. All benzodiazepines increase the risk of cognitive impairment, delirium, falls, and fractures in the elderly. Benzodiazepine-induced delirium is often misdiagnosed as dementia, which may result in the inappropriate prescription of additional central nervous system medications such as antipsychotic drugs. Benzodiazepines and antipsychotic drugs such as chlorpromazine should almost always be avoided in the elderly; clinicians “should avoid antipsychotics for behavioral problems unless nonpharmacologic options have failed or are not possible and the older adult is threatening substantial harm to self or others.”¹⁰

Clinical Vignette: Metformin. A generally healthy 72-year-old man with mild, well-controlled hypertension

came to his primary care physician complaining of the recent onset of urinary frequency, nocturia, and dry mouth. He was moderately overweight and did not exercise regularly. There was a family history of type 2 diabetes mellitus in 2 siblings. Fasting blood sugar was 205 mg/dL. The physician made a diagnosis of type 2 diabetes mellitus and discussed possible exercise regimens with the patient; they agreed on a regimen of brisk 30-minute walks in the patient's neighborhood a minimum of 3 times a week. The patient and his spouse were also referred to a dietician for nutritional counseling.

On return visits over the next 3 months, the patient reported that he was following the prescribed diet fairly faithfully but admitted he was not reaching the exercise target regularly, which he blamed on inclement weather. His weight was unchanged, but his fasting blood sugar was slightly improved at 175 mg/dL. His urinary symptoms and dry mouth were also modestly improved. The physician prescribed immediate-release metformin 500 mg to be taken orally twice a day and directed the patient to increase the morning dose by 500 mg after 1 week and the evening dose by 500 mg after a second week.

The patient returned prior to his scheduled visit at the end of the third week complaining of nightmares, night sweats, palpitations, nausea, diarrhea, and a metallic taste in his mouth. It turned out that the patient had misunderstood the physician's instructions and had increased the dose by 500 mg twice daily after each of the first and second weeks, and was now taking a total of 3000 mg each day instead of the intended total daily dose of 2000 mg (the maximum recommended dose is 2550 mg daily). His fasting blood sugar was only 75 mg/dL.

The physician reduced the dose of metformin to 500 mg twice daily and scheduled a follow-up visit in 1 week. At that visit the patient reported that his nightmares, night sweats, and palpitations had stopped, and his other symptoms had improved. His fasting blood sugar was 150 mg/dL. After a further 2 weeks the nausea had resolved, but he was still having soft stools and the metallic taste, and his fasting blood sugar was 160 mg/dL. The physician reinforced the importance of exercise and proper diet and over the next 2 months gradually raised the metformin dose to 1000 mg twice daily, a total maintenance dose of 2000 mg daily. The patient reported that his stools were normal and the metallic taste had disappeared. Fasting blood sugars were consistently in the range of 110 to 120 mg/dL.

Commentary. This vignette illustrates some of the pitfalls of dosage adjustment that apply particularly to the elderly but also to patients in general.

Initiating a medication or changing its dose is an occasion fraught with potential errors. It is essential

that the patient understand what the medication is, what it is for, how much of it to take and when to take it, and what adverse effects to watch out for. Written instructions are often a good idea. In this case the patient's misunderstanding of the physician's instructions led to an excessive dose of metformin, which precipitated hypoglycemia during the long fast between the evening meal and the next morning, causing the symptoms of nightmares, night sweats, and palpitations. Hypoglycemia can be very dangerous and even fatal when severe.

The pace of dosage adjustment also contributed to the complications in this case. It would have been wise to check the patient's fasting blood sugar after initiating the medication and before adjusting the dose in order to appraise the effect of this particular medication in this particular patient. That approach would likely have avoided the progression to hypoglycemia. It might also have forestalled the development of nausea, diarrhea, and the metallic taste in the mouth, side effects of metformin that are in part dose related. Promptly reducing the dose of metformin alleviated the nocturnal hypoglycemia and terminated its symptoms. Dose reduction also helped to diminish the dose-related side effects. Slow up-titration of the dose then allowed the patient to become habituated to the medication. Some side effects will attenuate as the patient becomes habituated to the medication, and patients can be reassured that that is likely to happen when that is known to be the case, as seen here.³²

This case also illustrates the importance of nonpharmacologic therapies prescribed alone or in combination with medications. Proper diet and exercise are essential components of comprehensive therapy for diabetes and other conditions, and even when they are insufficient in themselves to fully control the condition, as in this case, they do potentiate drug therapy and often make it possible to use fewer drugs and lower doses, reducing costs and drug side effects.

Clinical Vignette: Treatment Guidelines. Mr O was an 86-year-old man who lived independently on a small farm near a major metropolitan area in the Midwest.³³ He had never had a serious illness, took no medications, and had not seen a doctor in years. He became a patient at a local clinic only when his 92-year-old brother, for whom Mr O served as caregiver, began to receive care there for a slowly progressive dementia. At Mr O's initial medical encounter his seated blood pressure (BP) was 150/96, and no significant abnormalities were identified on physical examination. His electrocardiogram was normal. Baseline laboratory studies included a random blood glucose of 180 mg/dL and serum creatinine of 0.9 mg/dL. A follow-up fasting blood glucose was 170 mg/dL, hemoglobin A1c was 8.5%,

and total cholesterol was 255 mg/dL. In accordance with established clinical guidelines, his physician initiated therapy for hypertension with an angiotensin-converting enzyme (ACE) inhibitor, for diabetes mellitus with metformin, and for hypercholesterolemia with lovastatin, and scheduled a follow-up visit in 3 months.

At the follow-up visit Mr O's seated BP was 150/95, fasting glucose 175, and hemoglobin A1c 8.3%. Total cholesterol was 195 mg/dL. Continuing to follow clinical guidelines, the physician added a thiazide diuretic and a second oral hypoglycemic agent. When Mr O began getting up every 2 hours to urinate at night, doxazosin was initiated. Soon after that he reported that he often became lightheaded on rising from the sitting position and also complained of fatigue because his sleep was so frequently disturbed by his nocturia. At the next clinic visit his seated systolic BP remained 150 and his A1c was 8.4%. Long-acting insulin was started, and a calcium-channel blocker was added to the antihypertensive regimen. Mr O soon developed nightmares and night sweats and noticed unsteadiness when he got up at night to urinate. He complained that with the copayments for his medications and clinic visits he could no longer afford beer and had cut back on his grocery purchases.

On the night before hospital admission, Mr O got up to urinate, became markedly lightheaded, fell, and broke his hip. After several hours he was able to crawl to the telephone and call 911. When the paramedics arrived Mr. O was confused; his systolic blood pressure was 80 mm Hg, and the diastolic BP was undetectable. Blood glucose was 40 mg/dL, and he was given 50% glucose solution with immediate improvement of all altered vital signs. On admission to the hospital he was alert and oriented and in pain from the broken hip. His serum creatinine was 1.5 mg/dL.

Later that day he underwent total hip arthroplasty under general anesthesia in a procedure lasting a little more than 2 hours. In the recovery room he was noted to have difficulty using his right hand and was dysarthric. During the next few hours it became clear that he had had a cerebrovascular accident during the surgical procedure. He had a stormy postoperative course with multiple complications including *C difficile* colitis and a rise in serum creatinine to as high as 3.5 mg/dL. He was eventually started on physical therapy and transferred to a rehabilitation facility. He remained there 3 months after the fall, by which time it was clear that he would never again be able to live independently. His savings had been exhausted by this time, and his brother with dementia had to be admitted to a nursing home as he no longer had a caregiver at home.

Commentary. For geriatricians this is an all-too-common story: the downward decline often seen when

elderly people are treated aggressively based on clinical guidelines that may not apply to them. The elderly are systematically excluded from most clinical trials, sometimes on the basis of arbitrary age cutoffs and sometimes on the basis of exclusion criteria that include conditions that are very prevalent in the elderly. Consequently, when evidence-based clinical guidelines are developed based on the results of large-scale clinical trials, the elderly are systematically underrepresented in the data on which the guidelines are based. Results obtained in middle-aged people who for the most part are healthy except for the condition under study cannot simply be extrapolated to the frail elderly with multiple comorbid conditions, although it is the elderly population that is most likely to have chronic medical conditions requiring treatment.^{8-10,34}

Results obtained in middle-aged people cannot be extrapolated to the elderly for several reasons. The elderly frequently have multiple comorbid conditions and are taking multiple medications. They absorb, metabolize, and excrete medications at different rates and sometimes by different pathways than younger patients do. They frequently respond differently to medications than younger patients do: elderly hypertensives, for example, respond better to diuretics and calcium channel blockers and less well to β -blockers and ACE inhibitors than younger patients do. The elderly have diminished physiologic reserve: heart, lung, liver, and kidney function all decline progressively with age even in the absence of disease. An 86-year-old with a normal serum creatinine when in homeostasis, such as Mr O, may have less than half of the total renal function of a healthy 25-year-old and may demonstrate rapidly deteriorating renal function when under physiologic stress. Older patients will also have diminished vascular compliance and are both resistant to antihypertensive treatment and prone to orthostatic hypotension. Blood pressure and heart rate should always be measured in the lying, sitting, and (especially) the standing position before starting, stopping, or changing antihypertensive medications in the elderly.

This case also illustrates some of the hazards of multidrug therapy. Mr O's nocturia was induced by the thiazide diuretic. Adding doxazosin to the ACE inhibitor and thiazide induced postural hypotension that was undetected by the physician and worsened by the further addition of a calcium channel antagonist, resulting in the fall and hip fracture. Addition of insulin to the oral hypoglycemic agents precipitated nocturnal hypoglycemia manifested by nightmares and night sweats, further impairing Mr O's sleep and contributing to his chronic fatigue. Although clearly well intentioned, the therapies prescribed impaired Mr O's quality of life and will probably hasten his demise. In

this case, as often in the elderly, less is more: *primum non nocere!*

Organ System Impairment Vignettes

Clinical Vignette: Acute Liver Disease and Warfarin Pharmacokinetics. A 76-year-old woman with a past medical history of hypertension (HTN), obesity, hyperlipidemia, and osteoarthritis presented to the hospital after a fall. She reported a mechanical fall, with no lightheadedness, dizziness, or loss of consciousness. The patient reported 8/10 pain in the right groin, worse with movement of her right leg. She was unable to ambulate. She denied chest pain, shortness of breath, nausea, vomiting, or abdominal pain. The patient reported well-controlled hypertension, stable hyperlipidemia, and no previous history of coronary artery disease (CAD). She reported good exercise tolerance prior to the fall. Her medication list included hydrochlorothiazide 25 mg daily, atorvastatin 20 mg daily, amlodipine 10 mg daily, and ibuprofen 400 to 600 mg twice per day (BID) as needed. The patient was a nonsmoker and reported social alcohol and no drug abuse. She had previous hysterectomy and cholecystectomy and reported no complications during or after these surgeries.

On admission, she was alert and oriented $\times 3$, in moderate distress due to the pain. Vital signs included temperature 36.8°C, BP 160/80 mm Hg, heart rate (HR) 76 beats/min, respiratory rate (RR) 16/min; SaO₂ (oxygen saturation) 97% RA (room air). She had a regular heart rhythm and rate with no murmurs. Chest and abdominal exams were unremarkable. She held the right leg in external rotation and abduction, with limited range of motion (ROM) due to the pain. There was no significant lower extremity edema on initial exam. Laboratory workup on admission was within normal limits with the exception of a platelet count of 110,000/mL. Electrocardiogram (ECG) showed normal sinus rhythm (NSR), and there were no significant ST-segment or T-wave changes. The patient had right hip and leg radiography positive for intertrochanteric hip fracture and was admitted to the internal medicine service. Orthopedic service was consulted.

The patient was placed at bed rest in Buck's traction; for pain control she was started on acetaminophen 1000 mg orally (PO) 3 times per day (TID), oxycodone 5 mg PO q4h (every 4 hours) as needed for moderate pain, and hydromorphone 0.5 mg IV q4h as needed for breakthrough pain. Sequential compression devices (SCDs) were applied for DVT (deep venous thrombosis) prophylaxis prior to her going to the OR. The patient was NPO (nothing per os) and started on IVF 75 mL/h NS (normal saline). Home medications were continued with the exception of ibuprofen. She underwent open reduction internal fixation on the next

day. The patient tolerated the procedure well. The day after surgery she was started on enoxaparin 30 mg subcutaneously (SC) daily for DVT prophylaxis. On day 4 postoperatively the patient developed significant right leg edema. Venous Doppler study was performed and revealed right popliteal vein DVT. Enoxaparin was changed from 30 mg daily to 1 mg/kg BID for full anticoagulation, and the same evening warfarin 5 mg PO was started with a plan to transition to oral anticoagulation prior to her discharge. The patient was recovering well and worked with physical therapy. She was discharged to home on postoperative day 5. On the day of discharge her INR (international normalized ratio) was 1.7, serum creatinine 0.9 mg/dL, blood hemoglobin 10 g/dL. Discharge medications included hydrochlorothiazide 25 mg PO daily; acetaminophen-oxycodone (325-5 mg) 1 to 2 tabs PO q4h PRN (as needed) for pain; warfarin 5 mg PO every evening; enoxaparin 70 mg SC BID; atorvastatin 20 mg PO daily; and amlodipine 10 mg PO daily. Her ibuprofen was stopped, and the patient was advised to avoid it while on warfarin due to an increased risk of bleeding. A prescription was given for a PT (prothrombin time)/INR in 5 days, and follow-up with her primary care physician was scheduled in 7 days.

However, after the discharge the patient's pain was not well controlled, and she could not work with physical therapy. The patient was advised by her physical therapist to also take over-the-counter pain medications, and she started to use extra strength (500-mg tablets) Tylenol[®] per the recommendations on the bottle up to 2 tabs q6h. Her follow-up INR on day 5 postdischarge was 2.3, and enoxaparin was stopped per her primary care physician's (PCP's) recommendations. The patient also complained to her PCP of abdominal bloating and nausea without emesis. This was thought to be secondary to pain medications and constipation. She was prescribed docusate 100 mg BID plus senna 2 tabs daily and advised to decrease oxycodone use. On the 10th day after discharge the patient developed epigastric pain. She was nauseated without emesis and developed diarrhea. The patient had a total of 3 black, liquid, and malodorous bowel movements (BM) over 14 hours and started to feel lightheaded, weak, and short of breath. The patient's husband noticed that she was lethargic and confused and brought her to the emergency room (ER). On initial evaluation she was found to be hypotensive with BP 89/45, HR 112, pale, and diaphoretic. The patient had another BM in the ER, which was identified as melena. The rest of the laboratory workup revealed serum creatinine 1.2 mg/dL, BUN 55 mg/dL, AST (aspartate aminotransferase) 10,471 IU/L, ALT (alanine aminotransferase) 3340 IU/L, alkaline phosphatase 105 IU/L, total bilirubin 3.8 mg/dL, albumin 2.8 g/dL, total protein

6.5 g/dL, PT 110s, INR 8.4, PTT (partial thromboplastin time) 150 seconds, blood hemoglobin 6.4 g/dL, hematocrit 17%, WBC (white blood cells) $7 \times 10^3/\text{mL}$, Plt (platelets) $108 \times 10^3/\text{mL}$. The serum acetaminophen concentration was elevated, 123 mg/dL. The patient was admitted to the intensive care unit (ICU), where she received a bolus of fluid for resuscitation, followed by FFP (fresh frozen plasma) and pRBC (packed red blood cells) transfusions. She received 5 mg vitamin K SC. The patient was started on a pantoprazole drip (continuous IV infusion), and Gastroenterology was consulted; she was also started on N-acetylcysteine per protocol for acetaminophen intoxication. She underwent esophagogastroduodenoscopy, which revealed a bleeding pyloric ulcer, treated with cauterization. No further bloody stools were observed after these interventions. The patient had an IVC (inferior vena cava) filter placed to prevent pulmonary embolus from the known DVT. Within 3 days she began to improve clinically and was discharged on day 10. However, liver function never fully recovered. The patient had a follow-up with the gastroenterologist, and further testing, including liver biopsy, raised the possibility of nonalcoholic steatohepatitis (NASH) as a predisposing condition that had not been recognized during her initial hospital admission. Once medically stable without signs of recurrent bleeding, the patient was placed back on anticoagulation with rivaroxaban.

Commentary. This is a classic case of acetaminophen-induced liver toxicity,³⁵ resulting in higher exposure to warfarin, which led to adverse events. The patient represented in the case is a woman who presented to the orthopedic service after a fall, resulting in a hip fracture. She had a history of hypertension, obesity, hyperlipidemia, and osteoarthritis. Based on this history, she also likely had chronic liver disease (NASH). She was started on a regimen to control her pain that included oxycodone, hydromorphone, and a total daily dose of acetaminophen of 3 g, including additional over-the-counter (OTC) Tylenol[®] as recommended by the physical therapist after her initial discharge. As a result of her hip fracture, she underwent a surgical procedure and was started on DVT prophylaxis with enoxaparin, followed by warfarin. Warfarin is an anticoagulant with a complicated dose-response relationship that requires constant clinical monitoring (INR) and dose adjustment to optimize therapy. Warfarin is a natural product, provided as a racemic mixture of R and S stereoisomers. Warfarin is predominately metabolized in the liver by multiple enzymes (CYP2C9 is responsible for metabolism of the more potent S stereoisomer).

High-dose acetaminophen-induced liver disease has been well characterized. Acetaminophen is metabo-

lized in the liver to a toxic metabolite, N-acetyl-p-benzoquinone-imine (NAPQI), which is normally immediately conjugated with glutathione, preventing hepatic toxicity. However, when administered at high doses, either acutely or chronically, the amount of NAPQI produced exceeds glutathione availability and binds to the hepatocyte, leading to liver injury. In the case outlined above, markers of liver function were significantly elevated (AST 10,471 IU/L, ALT 3340 IU/L, AlPhos 105 IU/L, total bilirubin 3.8 mg/dL). Drug-induced liver disease results in numerous pathophysiological changes in the liver that can influence drug disposition, that is, pharmacokinetics. In the case presented here we observed an increase in the INR up to 8.4, which may have been a result of increased warfarin exposure in this patient. There is also evidence that acetaminophen can directly have an effect on clotting factors, resulting in an increase in INR, in addition to altering warfarin PK; however, for the purposes of this case, we focus on the effects of drug-induced liver injury on warfarin PK and subsequently the INR. This case provides evidence that knowledge about treating elderly patients with drugs that can potentially result in acute liver injury and the downstream effects on the PK of concomitant medications in the course of a complicated hospital stay can prevent adverse events.

Clinical Vignette: Vancomycin Toxicity in Adults. A 71-year-old gentleman with a history of poorly controlled diabetes mellitus type 2 (DM2), coronary artery disease (CAD), peripheral neuropathy, and of peripheral vascular disease status post left below-knee amputation (BKA) due to osteomyelitis presented to the emergency department (ED) with a right heel wound, present for a month, resulting in a black eschar. On the day of admission the patient noticed bloody, malodorous discharge coming from the wound and erythema around the eschar. The patient denied any pain in the area but had chronic loss of sensation in both feet due to peripheral neuropathy. He denied any fever, chills, nausea, vomiting, diarrhea, dysuria, chest pain, or shortness of breath. In the ED the patient was afebrile and hemodynamically stable with BP 126/51 mm Hg, HR 80 beats/min, respiratory rate 16/min, oxygen saturation (SaO₂) 99% on room air, and weight of 130 kg. He was alert and oriented, conversant, and in no acute distress. Chest exam revealed regular heart rhythm and rate with no murmurs. Bibasilar crackles were appreciated on lung auscultation. Chronic venous stasis changes were observed over his right lower extremity with scaling. He had a large 5-cm-diameter eschar over his right heel with serosanguineous malodorous discharge coming from the sides of the eschar. Laboratory workup revealed blood glucose 409 mg/dL, WBC (white blood cells) $10.6 \times 10^3/\text{mL}$; serum lactate

2.0 mmol/L; C-reactive protein (CRP) 9.95 mg/dL; BUN 32 mg/dL and a serum creatinine 1.5 mg/dL, which was his previous baseline. Radiography of the right foot and ankle revealed soft tissue ulceration overlying the posterior calcaneal tuberosity with soft tissue gas extending inferiorly just at the depth of the skin. There was no deep soft tissue gas or evidence of osteomyelitis. Vascular Surgery was consulted for gangrene and recommended antibiotics with a plan for surgical intervention. Given his prior history of MRSA (methicillin resistant staphylococcus) infection, the patient was started on vancomycin 2 g IV q12h, piperacillin-tazobactam 4.5 g IV q6h, and clindamycin 600 mg IV q6h. The patient was taken to the OR on day 2 after admission and underwent a right below-knee amputation. His home medications were continued, including amlodipine 10 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, furosemide 20 mg daily, gabapentin 300 mg TID, hydrochlorothiazide 12.5 mg daily, insulin glargine 40 units SC daily, insulin lispro 0 to 18 units per sliding scale q6h, lisinopril 2.5 mg daily, and metoprolol 50 mg BID. The patient had an uneventful immediate postoperative course. On day 3 postadmission his serum creatinine was found to be 2 mg/dL. He had good urinary output, and the rest of the laboratory workup was in the normal range excluding an elevated blood glucose level. On day 5 postadmission, BUN was 38 mg/dL, serum creatinine 2.8 mg/dL, serum potassium 5.1 mmol/L, and the rest of the laboratory workup was stable. A random serum vancomycin level was ordered and was found to be elevated at 38 mg/L. His vancomycin was placed on hold. During the early morning on day 6 of admission, his nurse noticed frequent paroxysmal ventricular complexes (PVCs) on the cardiac monitor and alerted the on-call physician. Blood was obtained from the patient for emergent determinations of his serum potassium, magnesium, and troponin levels. The patient was alert and oriented but reported palpitations, lightheadedness, and shortness of breath but denied chest pain. He reported that he had been getting more short of breath during the previous day. Pulse oximetry was declining over the last evening, and the nurse had placed him on 2 L/min of oxygen via a nasal cannula. The nurse also pointed out that the patient had had only 50 mL urinary output during the previous 8-hour shift. During the on-call physician's evaluation the patient was found to have an SaO₂ of 89% on 2 L/min O₂, and his O₂ "dose" was increased to 6 L/min O₂ via nasal cannula. The rest of his vital signs were BP 170/95 mm Hg, HR 89 beats/min and irregular, temperature 37.1°C, and respiratory rate 24/min. During evaluation, the patient lost consciousness and developed ventricular tachycardia, and condition C (announcement of an emergent situation, patient in a cardiopulmonary

arrest, requiring a team of providers to rush to the bedside and initiate immediate resuscitation) was initiated. His serum potassium concentration was elevated to 6.5 mmol/L, BUN 42 mg/dL, serum creatinine 3.2 mg/dL, serum magnesium level 2.3 mmol/L, and troponin I <0.1. Chest radiography revealed pulmonary edema. The patient was successfully resuscitated, treated for hyperkalemia, and transferred to the intensive care unit. Lisinopril and vancomycin were stopped. Over the next 7 days off vancomycin, his renal function gradually improved. His urinary output improved, and with supportive care the patient recovered without initiation of hemodialysis. The patient was transferred to a skilled nursing facility for further rehabilitation.

Commentary. This case provides an example of both the effect of CKD on drug disposition as well as drug-induced AKI.^{16,17} This case provides a classic example of alterations of vancomycin exposure due to CKD and resulting toxicity as a result of these higher exposures. More than 80% of a vancomycin dose is excreted unchanged in the urine within 24 hours after administration. Dose adjustments of vancomycin are recommended in patients with kidney disease, which is typically done by extending dosing intervals in patients with decreases in creatinine clearance (CrCL). The patient in this case had underlying mild CKD (serum Cr of 1.5 mg/dL; estimated CrCL of ~80 mL/min) most likely due to underlying DM2. The patient was started on a regimen for suspected MRSA, with a starting dose of vancomycin of 2 g IV q12h. The random serum vancomycin concentration came back high (38 mg/L), and the drug was then put on hold. Due to his underlying mild CKD, a dose adjustment of vancomycin would have been warranted to a dosing frequency every 24 hours.

This case also reveals that underlying kidney function during admission began to decrease with serum Cr levels of 2.0 mg/dL on day 3 postadmission, 2.8 mg/dL on day 5 postadmission, and 3.0 mg/dL prior to resuscitation. Our sample case provides a clear example of a patient with underlying CKD, treated with higher dose vancomycin resulting in higher serum vancomycin concentrations, in turn resulting in deteriorating kidney function.

Conflict of Interest

The authors have no conflict of interest to report relative to this paper.

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