



# Drug Dosing in Special Populations: Obesity and Geriatrics

By Jeffrey F. Barletta, Pharm.D., FCCM

Reviewed by: Matthew J. Felbinger, Pharm.D., BCPS; Bradley J. Peters, Pharm.D., BCPS, BCCCP; and Zachary R. Smith, Pharm.D., BCPS, BCCCP

## LEARNING OBJECTIVES

1. Compare and contrast the pharmacokinetic variability in patients with extreme obesity with that in individuals with normal body habitus.
2. Develop a strategy for dosing medications when information in the available literature is limited.
3. For patients with extreme obesity, develop a dosing strategy for sedatives, analgesics, vasopressors, anticoagulants, and antimicrobials.
4. Compare and contrast the pharmacokinetic variability in older adult patients with that in non-older adult patients.
5. Evaluate medication-specific considerations for older adult patients who are prescribed sedatives, analgesics, antipsychotics, anticoagulants, GI medications, or antimicrobials.

### ABBREVIATIONS IN THIS CHAPTER

AdjBW	Adjusted body weight
IBW	Ideal body weight
LBW	Lean body weight
MAP	Mean arterial pressure
PPI	Proton pump inhibitor
TBW	Total body weight
t>MIC	Time above MIC
Vd	Volume of distribution
VTE	Venous thromboembolism

[Table of other common abbreviations.](#)

## OBESITY

Recent statistics show a 39.8% prevalence of obesity among U.S. adults, with a rising trend from previously published data in 1999 (Hales 2017). Furthermore, 7.7% of adults, or 1 in 13, have extreme obesity, defined as a BMI of 40 kg/m<sup>2</sup> or greater. Crafting dosing regimens in this population can be challenging, given the pharmacokinetic variability that exists and that these patients are not typically represented in clinical trials. Few resources are available to guide clinicians in this setting. One study evaluated product information and pivotal studies of intravenous medications to determine whether a specific weight descriptor was included (Jacques 2010). Of 84 medications evaluated, only 27% had some reference to a weight descriptor. A follow-up conducted about 10 years later evaluating 100 of the most commonly used intravenous medications in the critical care setting showed that only 30 had some reference to a weight descriptor (Eastman 2020). Nevertheless, clinicians must still derive dosing regimens for these patients, often resorting to pharmacokinetic studies, retrospective analyses, or physicochemical characteristics of medications.

### Size Descriptors

Body size and shape, also known as habitus, refer to physical attributes of individuals such as height, weight, and body proportions. The measure of these attributes is termed *anthropometry*. In general, body composition compartments consist of fat mass and fat-free mass. Fat-free mass can further be stratified to include total body protein, intra- and extracellular water, and bone tissue (Thibault 2012). Changes in body habitus secondary to weight gain have variable

influence on the volumes of each of these compartments, which can influence drug pharmacokinetics. As fat mass is added, a concomitant, non-proportional increase in fat-free mass by about 25% occurs that is metabolically active (Heymsfield 2014). Furthermore, the physiologic activity of fat mass can vary depending on the specific type (brown vs. white) and the relative distribution (waist vs. hips) (Booth 2014; Chechi 2014).

Several sophisticated methods exist to quantify fat mass versus fat-free mass. These include bioelectrical impedance, dual x-ray absorptiometry, and CT. However, these techniques have not been well studied in hospitalized patients and may not be practical for the ICU (Sheean 2020; Mundi 2019). The most common size descriptors used in clinical practice are based on height, weight, and sex (Table 1).

The WHO uses BMI to characterize obesity (Table 2).

*Body mass index* represents the ratio of total body weight (TBW) to height squared but does not differentiate fat mass from fat-free mass; therefore, BMI is not intuitively useful for drug dosing (Gonzalez 2017). Body surface area is considered

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Pharmacokinetic alterations that occur because of critical illness
- Pharmacodynamic end points that are targeted in critically ill patients
- Basic physiologic alterations that occur secondary to obesity and aging

*Table of common laboratory reference values.*

### ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Roberts JA, Kumar A, Lipman J. [Right dose, right now: customized drug dosing in the critically ill.](#) Crit Care Med 2017;45:331-6.
- Smith BS, Yogaratnam D, Levasseur-Franklin K, et al. [Introduction to drug pharmacokinetics in the critically ill patient.](#) Chest 2012;141:1327-36.
- Roberts JA, Lipman J. [Pharmacokinetic issues for antibiotics in the critically ill patient.](#) Crit Care Med 2009;37:840-52.
- Schetz M, De Jong A, Deane AM, et al. [Obesity in the critically ill: a narrative review.](#) Intensive Care Med 2019;45:757-69.
- Pisani MA. [Considerations in caring for the critically ill older patient.](#) J Intensive Care Med 2009; 24:83-95.

**Table 1.** Equations for Estimating Body Size

Size Descriptor	Equation
Body mass index (kg/m <sup>2</sup> )	TBW/height (m) <sup>2</sup>
Body surface area (m <sup>2</sup> ) (Mosteller)	$\sqrt{[(\text{height (cm)} \times \text{TBW})/3600]}$
Body surface area (m <sup>2</sup> ) (DuBois)	$\text{TBW}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$
Ideal body weight (kg) (Devine)	Males: 50 kg + 2.3x (inches > 60) Females: 45.5 kg + 2.3x (inches > 60)
Lean body weight (kg) (Janmahasatian)	Males: (9270 × TBW)/ (6680 + 216 × BMI) Females: (9270 × TBW)/ (8780 + 244 × BMI)
Adjusted body weight (kg) (Bauer)	CF (TBW – IBW) + IBW

CF = correction factor (most commonly = 0.4); IBW = ideal body weight (kg); TBW = total body weight (kg).

Information from: Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098; DuBois D, DuBois EF. Clinical calorimetry. Tenth paper. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863; Devine BJ. Case number 25: gentamicin therapy. Drug Intell Clin Pharm 1974;8:650-5; Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44:1051-65; Bauer LA, Edwards WA, Dellinger EP, et al. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol 1983;24:643-7.

the gold standard for dosing chemotherapy medications but is not routinely used in critical care. In the ICU, weight-based dosing is typically performed using either TBW or an alternative such as ideal body weight (IBW), lean body weight (LBW), fat-free mass, or adjusted body weight (AdjBW).

*Lean body weight* appears to be the best representation of fat-free mass, and these terms are often considered interchangeable. However, there are minor differences, given that LBW also includes lipids in the cellular membranes, CNS, and bone marrow, which is about 3%–5% of TBW (Janmahasatian 2005). Several equations exist to estimate LBW, but they may underestimate LBW when extrapolated to patients with extreme obesity (Han 2007). In the most accurate formula, LBW continues to rise as body weight increases; this better reflects the increase in lean tissue (i.e., fat-free mass) that occurs with increased fat mass (Janmahasatian 2005). This formula may be difficult to implement at the bedside, so some form of automated software program should be used to avoid calculation errors.

**Table 2.** WHO Obesity Classifications

Body Mass Index (kg/m <sup>2</sup> )	Classification
< 18.5	Underweight
18.5–24.9	Healthy weight
25–29.9	Overweight
30–34.9	Obesity class I
35–39.9	Obesity class II
≥ 40	Obesity class III (also called extreme obesity)

Information from: World Health Organization (WHO). [Obesity](#).

*Ideal body weight* is another weight metric commonly used for medication dosing and is sometimes used as a surrogate for LBW. Ideal body weight is inherently flawed, though, because it is solely a function of height and sex. Ideal body weight was derived from insurance data from more than 60 years ago on the premise that, for a given height, there is a desired or ideal weight (Pai 2000). Ideal body weight does not account for differences in body composition or increases in lean body mass that occur with increases in fat mass. Thus, the potential for underestimating weight (and weight-based doses) exists if IBW is used as a surrogate for LBW.

One of the most common measures used for drug dosing is AdjBW using some “correction factor.” These formulas were originally proposed from studies describing aminoglycoside dosing whereby some fraction of the difference between TBW and IBW (i.e., the correction factor) was added to IBW. The most common correction factor is 0.4, but wide variability has been reported (range 0.14–0.98) (Pai 2012). Although it is reasonable to consider AdjBW for dosing medications in patients with extreme forms of obesity, clinicians should consider this variability (with correction factor) coupled with the limitations of using IBW as its root.

Another technique is based on principles of allometry and dose scaling. Allometry is the study of the relationship between body size and physiology. Allometry accounts for the nonlinear relationship that exists between size and physiologic variables that influence drug pharmacokinetics. Allometric scaling involves taking a pharmacokinetic or physiologic variable scaled to weight raised to a particular exponent. An exponent of 1 implies a linear relationship, whereas an exponent of 0 indicates weight independence. A common scaler used is 0.75 of the standard weight-based dose, which is thought to represent the basal metabolic rate in animals (Pai 2012). The dose is calculated as follows: allometric dose = standard dose × [TBW (obese)/TBW (standard)]<sup>β</sup>, where “β” is the allometric scaler. For example, if the dose of a medication for a patient weighing 75 kg is 1000 mg

and the weight scaler is 1, the dose for a patient weighing 150 kg (presuming all other variables are constant) is 2000 mg. In contrast, if a scaler of 0.75 is used, the dose is 1682 mg. Although this method is not widely used in the clinical setting, reports of drug dosing are emerging (Brown 2017).

### Pharmacokinetic Considerations

Drug distribution depends on the physiochemical properties of the drug (lipophilicity, ionization, molecular size), the physical and chemical properties of the tissue, plasma protein binding, and tissue perfusion (Morrish 2011). Obesity is associated with absolute increases in adipose tissue mass, lean body mass, organ mass, blood volume, and cardiac output; volume of distribution (Vd) values are therefore largely affected. Volume of distribution is the most influential parameter when single or isolated doses are administered such as a loading dose. Drugs with a small Vd are normally hydrophilic and do not distribute widely into secondary compartments (e.g., adipose tissue). In general, these medications are expected to require loading doses on the basis of LBW. In contrast, drugs with a large Vd tend to be more lipophilic and distribute extensively into adipose tissue or other areas of the body. These medications are expected to require loading doses on the basis of either AdjBW or TBW. However, there are exceptions to this generalization. First, digoxin has a large Vd (about 500 L) because it has a high affinity for cardiac and skeletal muscle. Drug distribution in this case is proportional to LBW, not TBW (Abernethy 1981). Second, for drugs with dose-related adverse effects, smaller doses that can be repeated may be safer than a single dose that is based on TBW. Clinicians must use caution with generalizations derived from assumptions made with Vd, particularly when Vd is large.

The second pharmacokinetic factor used to describe drug disposition is clearance. Clearance is a primary factor that influences the maintenance dose for a medication. Obesity is associated with increased kidney mass and blood flow; thus, clearance is expected to increase. However, this change is not proportional to TBW, and studies describing drug clearance have had mixed results. Additional comorbidities that typically accompany obesity (e.g., hypertension, diabetes) may explain these mixed results.

Drug clearance is commonly estimated using the Cockcroft-Gault equation (Cockcroft 1976). This equation was validated in a predominantly male cohort with normal body habitus. The equation is inherently inaccurate when used in patients with extreme obesity, particularly when TBW is used in the calculation (Demirovic 2009). One study measured the bias and accuracy of the various formulas used to estimate CrCl with different weight metrics in a cohort of non-ICU, hospitalized patients with a mean BMI in excess of 50 kg/m<sup>2</sup>. The most accurate estimate was LBW using the LBW formula (see Table 1) (Janmahasatian 2005). Using TBW in the Cockcroft-Gault formula overestimated the CrCl by

about 2-fold, whereas IBW underestimated the CrCl by about 22%. Adjusted body weight with a 40% correction factor overestimated the CrCl by 30%.

In addition to the variability in pharmacokinetics associated with obesity, clinicians must consider the variability associated with critical illness. For example, Vd is larger (secondary to increased total body water) and has much greater variability in the ICU. Volume of distribution often changes during hospitalization as critical illness subsides and de-resuscitation occurs. Clearance can be affected by several factors, including end-organ dysfunction, accumulation of active metabolites, and augmented renal clearance. These factors are generally absent in most pharmacokinetic studies of patients with obesity but must be considered when making dosing decisions in the ICU.

### General Dosing Principles

Formal dosing recommendations for medications commonly used in critically ill patients with extreme obesity are lacking, but a general framework has been proposed (Erstad 2015). The first step is to evaluate the patient's weight. For patients who are overweight or have mild obesity (e.g., class I, BMI less than 35 kg/m<sup>2</sup>), the doses recommended in either the product label or a reputable tertiary reference are usually appropriate because these patients were likely well represented in the studies that led to the dosing information provided. Dosing becomes more complicated in patients with extreme forms of obesity (e.g., class III, BMI 40 kg/m<sup>2</sup> or greater) because these patients are often excluded from studies or are so underrepresented that no meaningful conclusions can be made. When this occurs, clinicians should search the literature for clinical and/or pharmacokinetic studies evaluating the particular medication in patients with extreme obesity (i.e., class III). Careful scrutiny is necessary to ensure that the weight range

of the patients included in the study is consistent with the weight of the patient in question. Clinicians must also review the study details, such as the number of patients evaluated, the concentrations that were measured (e.g., free vs. total, serum vs. tissue), and the specific pharmacodynamic goal that was chosen (e.g., 40% vs. 100% time above MIC [ $t > MIC$ ]). As with all primary literature, the quality and generalizability of the data must be assessed.

When clinical investigations reporting outcomes are available and the study population includes the patient in question, the dosing used in the study may be appropriate. In most cases, however, clinical trials are not available, and the clinician must resort to pharmacokinetic studies. When relying on pharmacokinetic studies, clinicians should assess for dose proportionality. Dose proportionality implies that the ratio increase in weight between the obese and non-obese populations is about the same as the ratio increase in Vd and clearance (not adjusted for weight). If dose proportionality is evident, weight-based dosing using TBW may be acceptable, pending the assessment of risk with a single large dose. However, most drugs that are renally cleared do not have properties of dose proportionality. In these cases, an alternative such as LBW or AdjBW may be preferred. Table 3 presents hypothetical examples of dose proportionality.

If no studies for that agent are available, clinicians can review dosing studies for medications in the same drug class that may have similar pharmacokinetic and physicochemical parameters (e.g., one cephalosporin for another). If this is not possible, clinicians must decide whether an alternative agent for which more data are available is appropriate. This should especially be considered with medications that have a high adverse effect profile or a narrow therapeutic index. In these situations, most individuals take a conservative approach with dosing to minimize adverse drug effects; however, this

**Table 3.** Hypothetical Examples Evaluating the Presence of Dose Proportionality

Example	Group	Weight Reference (kg)	Volume of Distribution (L)	Vd Indexed to TBW (L/kg)	Creatinine Clearance (mL/min)	CrCl Indexed to TBW (mL/kg/min)	Dose Proportionality?
1	1	70	45	0.64	70	1	No
	2	140	60	0.43	120	0.86	
2	1	80	100	1.25	80	1	Yes
	2	120	150	1.25	120	1	
3	1	75	80	1.07	100	1.33	Yes, for Vd No, for clearance
	2	150	156	1.04	109	0.73	
4	1	60	7	0.12	12	0.2	No
	2	120	10	0.08	14	0.12	

Vd = volume of distribution.

can also lead to delays in reaching target concentrations and possibly treatment failure.

The final step is to evaluate whether the benefits of larger doses (i.e., using TBW for weight-based dosing or the higher end of the usual dosing range for non-weight-based dosing) outweigh the risks of overdosing or an adverse effect. In some cases, an alternative strategy that prioritizes safety may be preferred, regardless of the conclusion from pharmacokinetic studies. An example is with midazolam in a nonintubated patient for a procedure. Midazolam is highly lipophilic with a large Vd. Pharmacokinetic studies suggest that TBW is preferred for initial doses. However, high midazolam doses are associated with cardiovascular adverse events, and overdosing can lead to respiratory depression and intubation. In this case, a series of smaller doses that can rapidly be titrated to effect would be preferred.

## Medication-Specific Recommendations

### Sedatives

Propofol or dexmedetomidine is recommended over benzodiazepines in the evidence-based guidelines for sedation in critically ill adults who are mechanically ventilated (Devlin 2018). Propofol is a highly lipophilic compound with a large Vd (about 60 L/kg) and a short half-life (DrugBank). No studies, however, evaluate propofol dosing in ICU patients with obesity for whom light sedation and comfort, in particular, are the goals. Several studies have described propofol dosing in the operating room for the induction and maintenance of anesthesia. One study reported a significant correlation with weight and both Vd ( $r=0.69$ ) and clearance ( $r=0.76$ ), indicating that TBW is the most appropriate weight measure (Servin 1993). However, other studies have described a nonlinear relationship between weight and clearance and suggest alternatives such as LBW or AdjBW as the preferred metric. In fact, one trial reported lower bispectral index values in populations with obesity that were dosed using TBW, implying that concentrations will be higher with this method (Dong 2016). Because propofol can rapidly be titrated to effect and because hypotension often occurs with large doses, weight-based dosing using either IBW or AdjBW is preferred.

Dexmedetomidine is also a lipophilic compound with a large Vd (118 L) (DrugBank). Similar to data analyses with propofol, most data analyses with dexmedetomidine originate in the operating room setting (Rolle 2018; Xu 2017; Cortinez 2015). Collectively, these data analyses show that dexmedetomidine pharmacokinetics are characterized best with fat-free mass and dosing using TBW results in higher serum concentrations. Weight-based dosing for dexmedetomidine should therefore be use either IBW or AdjBW.

Benzodiazepines are also highly lipophilic, and marked differences in pharmacokinetic variables have been noted in individuals with obesity. In one study, midazolam Vd was significantly larger in patients with obesity (311 L vs. 114 L) but with no difference in CrCl (472 mL/minute vs. 530 mL/minute)

(Greenblatt 1984). The elimination half-life was significantly longer in the obese cohort (8.4 hours vs. 2.7 hours). A second study described a linear increase in central Vd with increasing weight but a nonlinear increase in peripheral Vd (Brill 2014). No difference was noted with CrCl. Midazolam has a larger Vd in patients with obesity, which suggests that larger doses are necessary in these patients than in their non-obese counterparts. However, large, single doses may lead to more adverse drug effects. Thus, for initial bolus doses, the safest approach is to use either a fixed dosing strategy (i.e., non-weight based) similar to that used in non-obese patients or a weight-based strategy using IBW or AdjBW. Smaller supplemental doses can then be repeated as needed until the desired effect is achieved. Because there is no difference in clearance, the duration of effect can be prolonged with repeated dosing or continuous infusions.

### Analgesics

All opioid analgesics are lipophilic, with some degree of variability across this class of medications (fentanyl > hydromorphone > morphine) (DrugBank). Although this suggests that TBW is the most appropriate weight measure for dosing, many studies have shown no relationship between analgesic response and weight (Patanwala 2014; Xia 2014; Bennett 1982). One study comparing the morphine pharmacokinetics in patients with morbid obesity with those in healthy volunteers showed no difference in clearance of the parent compound, but the obese cohort had decreased clearance of active metabolites (de Hoogd 2017). Studies with fentanyl, one of the most lipophilic opioids, have shown a nonlinear relationship between clearance and TBW and have concluded that dosing on the basis of TBW leads to excessive dosing (Shibutani 2005, 2004). Guidelines from Great Britain and Ireland on the perioperative management of surgical patients with obesity recommend LBW as a starting point for opioid dosing because the clinical effect is poorly related to plasma concentrations, and the medication can be titrated to effect (Nightingale 2015). Dosing strategies for all opioids should therefore either be non-weight based, using doses similar to those used in non-obese patients, or weight based, using IBW or AdjBW. Specific opioid selection should also consider other patient-specific characteristics similar to non-obese patients (e.g., choosing hydromorphone over morphine in patients with renal insufficiency).

### Vasopressors

Vasopressors like norepinephrine are cornerstones of therapy for providing hemodynamic support in shock. All vasopressors are hydrophilic agents with a small Vd, suggesting minimal distribution beyond the vasculature. Weight is therefore expected to have an insignificant effect on response. Regardless of obesity, there is substantial interpatient variability between catecholamine dose and response (Wacharasint 2013; Beloeil 2005; Johnston 2004). One study reported

unpredictable norepinephrine pharmacodynamics whereby drug concentrations were not correlated with changes in mean arterial pressure (MAP) (Beloeil 2005). Another study reported that patients with obesity received less fluid and less vasopressor therapy when the dose was normalized to weight (supporting non-weight-based dosing). Mortality at 28 days was lower in the obese cohort (Wacharasint 2013). Major prospective clinical trials evaluating vasopressor therapy in shock have used both weight-based and non-weight-based dosing regimens (Khanna 2017; Gordon 2016; De Backer 2010; Russell 2008; Annane 2007).

Retrospective studies have evaluated dosing strategies for norepinephrine in the obese population. One study reported similar norepinephrine dosing requirements (not adjusted for weight) between patients with obesity and non-obese patients, with no difference in MAP (Radosevich 2016). A second study showed no difference in the time to goal MAP between weight-based and non-weight-based dosing strategies (Vadiei 2017). Furthermore, with weight-based dosing, the median cumulative dose was higher, and the time to therapy discontinuation was longer. Collectively, these studies show that a weight-based dosing strategy with norepinephrine is unnecessary and may lead to increased drug exposure if TBW is used. Either fixed, non-weight-based dosages of norepinephrine or a weight-based dose using IBW is recommended. Studies evaluating other catecholamine infusions (e.g., epinephrine, dopamine) are limited; however, a similar recommendation would apply for these agents.

The impact of obesity has also been evaluated with vasopressin dosing. One retrospective study showed no significant differences in the change in MAP after a fixed dose of vasopressin across four BMI categories (Lam 2008). A second retrospective study found no significant correlation between BMI and the change in MAP at either 1 hour ( $r = -0.230, p = 0.68$ ) or 6 hours ( $r = -0.288, p = 0.52$ ) (Hodge 2016). A significant correlation was observed between BMI and change in MAP at 6 hours in the patient subgroup with BMIs above  $30 \text{ kg/m}^2$  ( $r = -0.951, p = 0.0009$ ). A third retrospective study reported a significant correlation between vasopressin dose, normalized to TBW, and the change in norepinephrine requirements ( $r = -0.46, p < 0.001$ ) (Miller 2012). Collectively, these studies show that some patients with obesity have a dampened response to vasopressin, but the impact of weight is inconsistent. Furthermore, there is wide interpatient variability with vasopressin response across all weight categories, and the cumulative sample size is small. Fixed, non-weight-based doses are therefore recommended with vasopressin.

## **Anticoagulants**

### **Low-Molecular-Weight Heparin: VTE Prophylaxis**

Obesity is a well-known risk factor for venous thromboembolism (VTE) in hospitalized patients (Kahn 2012). One study reported a significant increase in both proximal deep venous

thrombosis (HR [95% CI] = 1.18 [1.04–1.35]) and pulmonary embolism (HR [95% CI] = 1.37 [1.02–1.83]) with each 10-point increase in BMI (Lim 2015). Prophylaxis for VTE is usually provided with low-molecular-weight heparin or unfractionated heparin. Low-molecular-weight heparin is preferred in most ICUs and has been suggested in recent evidence-based guidelines (Schunemann 2018). In addition, one large registry study reported a lower incidence of VTE with low-molecular-weight heparin than with low-dose unfractionated heparin in patients after bariatric surgery (OR [95% CI] = 0.34 [0.19–0.62]) (Birkmeyer 2012). The most appropriate dosing strategy, however, has been widely disputed. Doses recommended in most tertiary references are fixed doses that are not based on weight. An inverse linear relationship exists between anti-factor Xa (anti-Xa) concentrations and weight (Frederiksen 2003). Doses extrapolated from non-obese patients may be suboptimal.

Few studies describe low-molecular-weight heparin dosing strategies that report VTE occurrence as the primary outcome. One investigation was a before-after study comparing a higher enoxaparin dosage (40 mg twice daily) with standard dosing (30 mg twice daily) in a cohort of bariatric surgery patients with an average BMI of about  $50 \text{ kg/m}^2$  (Scholten 2002). The VTE rate was significantly reduced with the higher dose (5.4% vs. 0.6%,  $p < 0.01$ ). Another retrospective study evaluated “high-dose” prophylaxis in 3928 hospitalized patients with a BMI of  $40 \text{ kg/m}^2$  or greater (Wang 2014). High-dose prophylaxis was defined as either 80 mg/day of enoxaparin or 22,500 units/day of unfractionated heparin. The VTE rate with high-dose prophylaxis was 0.77% compared with 1.48% with standard dosing (OR [95% CI] = 0.52 [0.27–1.00]). No difference in bleeding was reported. Of note, these studies were not specific to ICU patients; thus, pharmacokinetic variability in critical illness (e.g., impact of vasopressor therapy, edema) is not well represented.

Some data analyses include critically ill patients, describing anti-Xa concentrations with low-molecular-weight heparin using alternative dosing strategies. One study evaluated surgical ICU patients with an average BMI of  $46.4 \text{ kg/m}^2$  who received weight-based dosing of enoxaparin  $0.5 \text{ mg/kg}$  every 12 hours (Ludwig 2011). Twenty-three patients were included, with an appropriate anti-Xa concentration (0.2–0.5 IU/mL) detected in 91%. There were no episodes of major bleeding. A similar strategy was evaluated in a cohort of trauma patients with obesity having a mean BMI of  $35.3 \text{ kg/m}^2$  (Bickford 2013). The median injury severity score was 14 (interquartile range 12); thus, some (but not all) of these patients were presumably in an ICU. Overall, target anti-Xa concentrations (0.2–0.6 IU/mL) were reached in 86% of patients. A third study assessed a weight-based enoxaparin dosing algorithm whereby dose was stratified by risk (Parikh 2015). Patients designated as very high risk (e.g., hip or knee orthopedic surgery, multiple trauma) received  $0.5 \text{ mg/kg}$  twice daily, and moderate-high risk patients (e.g., general surgery or critically

ill patients) received 0.5 mg/kg daily. Collectively, anti-Xa concentrations were appropriate (0.2–0.6 IU/mL) in 85% of patients.

The remaining studies have evaluated alternative dosing strategies for enoxaparin in either a bariatric surgery population or generalized medical patients (i.e., non-ICU) (Miranda 2017; Freeman 2012; Rondina 2010; Borkgren-Okonek 2008; Rowan 2008; Simone 2008). Although most of these studies showed many patients achieving target anti-Xa concentrations, the dosing regimens used varied widely. For example, one prospective study evaluated anti-Xa concentrations in medically ill patients who were randomized to receive enoxaparin 0.5 mg/kg/day, 0.4 mg/kg/day, or 40 mg/day (Freeman 2012). The average BMI in this study exceeded 60 kg/m<sup>2</sup> for all three dosing groups. Target anti-Xa concentrations were achieved in significantly more patients receiving 0.5 mg/kg/day than in patients receiving the fixed dose or lower weight-based regimens. Another study evaluated enoxaparin dosing in bariatric surgery patients whereby patients with a BMI of 50 kg/m<sup>2</sup> or less received 40 mg twice daily and patients with a BMI greater than 50 kg/m<sup>2</sup> received 60 mg twice daily (Borkgren-Okonek 2008). Subtherapeutic anti-Xa concentrations were reported in 21% and 14% of patients, respectively, indicating that a higher dosing regimen was necessary when the BMI exceeded 50 kg/m<sup>2</sup>.

In summary, enoxaparin dosing varies widely in the obese population, with most studies reporting anti-Xa concentrations and not VTE rate. Furthermore, data analyses specific to critically ill patients are sparse. For patients with a BMI of 40 kg/m<sup>2</sup> or greater, 40 mg twice daily seems appropriate because this is the only dosing regimen shown to reduce the VTE rate. In patients with more extreme forms of obesity (i.e., BMI 50 kg/m<sup>2</sup> or greater), larger doses may be necessary. The most appropriate dose is unknown because dosing strategies in the literature consist of fixed doses (60 mg twice daily, equivalent to about 0.4 mg/kg/dose) and weight-based doses ranging from 0.5 mg/kg once daily to 0.5 mg/kg twice daily. Nevertheless, for critically ill patients with a BMI in excess of 50 kg/m<sup>2</sup>, a weight-based regimen of 0.4–0.5 mg/kg twice daily is reasonable. Given the lack of consistency with dosing suggestions across pharmacokinetic studies, anti-Xa monitoring can be considered.

### **Low-Molecular-Weight Heparin: Therapeutic Dosing**

Several pharmacokinetic studies describe weight-based dosing of low-molecular-weight heparin for the treatment of thromboembolic disease (Sebaaly 2018). Interpretation of these studies, however, is complicated by the paucity of patients with more extreme forms of obesity and the use of dose-capping strategies. Furthermore, data specific to the critically ill population are lacking.

Enoxaparin safety and efficacy were reported in a subgroup analysis of patients enrolled in two large trials of patients

with coronary artery disease (Spinler 2003). No difference in efficacy or major hemorrhage between patients with obesity and those without obesity was evident when enoxaparin was dosed using TBW. However, few patients with extreme obesity were included because the average weight and BMI in the obese cohort were 94 kg plus or minus 14 kg and 33.8 kg plus or minus 4 kg/m<sup>2</sup>, respectively. In contrast, a second study of patients with acute coronary syndromes suggested that bleeding rates are higher in patients with more extreme forms of obesity (Spinler 2009). Over 19,000 patients were categorized into four weight groups (less than 100 kg, 101–120 kg, 121–150 kg, and greater than 150 kg), and major bleeding rates were reported. In general, bleeding rates followed a U-shaped distribution and were highest in the cohort that weighed more than 150 kg. Patients in this cohort received a lower dose than recommended on the basis of TBW (1 mg/kg). In fact, when bleeding rates were compared between patients who received recommended doses (0.95–1.05 mg/kg) and those who received reduced doses (less than 0.95 mg/kg), recommended doses were associated with more than a 2-fold higher rate of bleeding; however, this was not statistically significant.

Other studies have evaluated anti-Xa concentrations in patients with obesity receiving weight-based enoxaparin dosing. Most studies have reported anti-Xa concentrations that were either therapeutic or supratherapeutic with doses less than the recommended dose (1 mg/kg) when TBW was used (van Oosterom 2019; Lalama 2015; Thompson-Moore 2015; Deal 2011). In fact, in one study, the median dose resulting in therapeutic anti-Xa concentrations was 0.83 mg/kg. Furthermore, the incidence of supratherapeutic concentrations was 71% with doses of 0.95 mg/kg or greater compared with 32% with doses less than 0.95 mg/kg ( $p=0.02$ ) (Thompson-Moore 2015). In a case report describing enoxaparin use for pulmonary embolism in a patient weighing 322 kg (BMI 114 kg/m<sup>2</sup>), therapeutic anti-Xa concentrations were reached with a dose of 0.62 mg/kg every 12 hours (Heitlage 2017). Another case report described enoxaparin dosing in a patient weighing 236 kg for whom a dose of 0.85 mg/kg every 12 hours was appropriate, on the basis of anti-Xa concentrations (Hanni 2019).

In summary, in patients with a BMI of 40 kg/m<sup>2</sup> or greater, weight-based doses using TBW that are lower than standard doses (1 mg/kg) appear to be appropriate. Data analyses are minimal for initial doses greater than 150 mg, given that most studies have used dose-capping strategies or have not included patients with weights that exceeded this value. Initial doses of 0.8 mg/kg every 12 hours may be reasonable. Lower doses may be required in patients with more extreme forms of obesity. A dose-capping strategy at 150 mg can be considered, given the limited published experiences with initial doses above this range. Anti-factor Xa monitoring is reasonable for therapeutic anticoagulation. In many situations, the safest strategy is to administer a continuous infusion of

unfractionated heparin. Unfractionated heparin offers the advantage of a shorter half-life, an effect that subsides more rapidly upon discontinuation and is reversed more efficiently with protamine, should bleeding occur. Studies have shown supratherapeutic activated PTT values when using TBW for unfractionated heparin dosing; thus, AdjBW is suggested (Fan 2016; Barletta 2008).

### **Antimicrobials**

Constructing an antimicrobial dosing regimen in critically ill patients requires careful evaluation of patient-specific pharmacokinetics, medication-specific pharmacodynamics, microbiology of the infectious organism, and location of the infection. In general, when a medication is administered, it will distribute and reach a certain concentration at an infection site. Ideally, these concentrations will be above the pharmacodynamic threshold associated with treatment success and successful patient outcomes will be recognized. Obesity leads to pharmacokinetic alterations that may result in lower peak concentrations or shorter  $t_{>MIC}$ . Clinicians must evaluate whether these pharmacokinetic alterations are substantial enough to affect achievement of the pharmacodynamic goals associated with success.

### **Penicillins, Cephalosporins, and Carbapenems**

Penicillins and cephalosporins are two of the most widely used drug classes for the empiric treatment of infections in the ICU. Penicillins and cephalosporins have time-dependent killing in which the goal is to maintain an adequate  $t_{>MIC}$  during the dosing interval. Piperacillin/tazobactam is one of the more widely studied penicillins in patients with obesity and critical illness (Alobaid 2017, 2016a; Jung 2017; Chung 2015; Sturm 2014; Cheatham 2013). Collectively, these data show an increase in both  $V_d$  and clearance. Several studies have reported pharmacodynamic target attainment using Monte Carlo simulations. One study of critically ill surgical patients evaluated the probability of target attainment after a 4.5-g dose every 6 hours administered as a 30-minute infusion (Sturm 2014). Nine patients with a mean weight of 164 kg plus or minus 50 kg were included, and the probability of target attainment (50%  $t_{>MIC}$  for an MIC of 16 mg/L) was 100% with all evaluated dosage regimens. Other studies have shown that prolonged or extended infusions may be preferred in this population, particularly when estimated CrCl or MIC values are higher (Alobaid 2017; Chung 2015; Cheatham 2013). In one study, piperacillin/tazobactam doses of 4.5 g every 8 hours administered over 4 hours were associated with greater than 90% target attainment (50%  $t_{>MIC}$ ), but doses of 3.375 g were not (Cheatham 2013). Similarly, a second study recommended initial regimens of 4.5 g every 8 hours infused over 4 hours for patients with a BMI of 30 kg/m<sup>2</sup> or greater compared with 3.375 g every 8 hours infused over 4 hours for non-obese patients (Chung 2015). Other studies have reported that extended or continuous infusions are

associated with an increased likelihood of achieving therapeutic concentrations and that intermittent dosing may be suboptimal in patients with higher MIC values and when CrCl is elevated (Alobaid 2017; Hites 2014, 2013). Creatinine clearance is a primary determinant of achieving target pharmacodynamic end points.

Cefepime pharmacokinetics have also been reported in patients with obesity. One study described a pharmacodynamic model using patient-specific pharmacokinetic data evaluating two dosing regimens: 2 g every 12 hours and 2 g every 8 hours (Rich 2012). Only the 2-g-every-8-hour regimen maintained the target 60%  $t_{>MIC}$  when the MIC was 8. Ceftazidime pharmacokinetics were evaluated in one study of normal weight and obese (class I, II, and III) individuals (Justo 2015). Both  $V_d$  and clearance were higher in the obese population ( $V_d$  36.4 vs. 45.3 L, CrCl 12 vs. 16.2 L/hour), but Monte Carlo simulations predicted that standard dosing (600 mg every 12 hours) would lead to a 90% probability of reaching 30%, 40%, and 50%  $t_{>MIC}$  for MICs of 2, 1, and 0.5 mcg/mL, respectively. This study was conducted in healthy volunteers, so the pharmacokinetic variability in critical illness was not represented.

Meropenem dosing regimens have been widely studied in the obese population (Chung 2017; Alobaid 2016a, 2016b; Pai 2015; Wittau 2015; Cheatham 2014; Kays 2014). Similar to other  $\beta$ -lactams,  $V_d$  and clearance are increased in obesity. Achievement of pharmacodynamic goals has varied across studies, largely secondary to the pharmacodynamic goal chosen (e.g., 100%  $t_{>MIC}$ , 40%  $t_{>MIC}$ ), organism MIC, CrCl, administration method (0.5- vs. 3-hour infusion), and range of weights included. In summary, meropenem concentrations depend more on CrCl, and obesity alone does not widely affect dosing (Alobaid 2016b). However, standard doses (1 g every 8 hours as a ½-hour infusion) may not achieve pharmacodynamic goals, particularly when targeting maximum pharmacodynamic end points in patients with higher CrCl values or with organisms having a high MIC. Prolonged infusions provide a significant advantage in this setting.

### **Quinolones**

Levofloxacin pharmacokinetics appear to be no different in patients with obesity than in non-obese individuals (Cook 2011). One study evaluated levofloxacin dosing in patients with a BMI of 40 kg/m<sup>2</sup> or greater who underwent therapeutic drug monitoring for dose optimization (Pai 2014). Levofloxacin AUC was not related to any body size metric but was inversely related to CrCl. A dosing algorithm was constructed, and the target AUC of 100 mg hour/L was not achievable with a 750-mg dose when CrCl exceeded about 90 mL/minute.

Ciprofloxacin disposition in obesity was evaluated in one study in which both  $V_d$  (269 vs. 219 L,  $p < 0.01$ ) and renal clearance (638 vs. 495 mL/minute,  $p < 0.05$ ) were increased in obesity (Allard 1993). This increase was not proportional to weight; thus, AdjBW using a correction factor of 0.45



was suggested. A second report described a patient weighing 226 kg who received a ciprofloxacin dose of 800 mg every 12 hours (Caldwell 1994). Therapeutic drug monitoring showed a peak serum concentration in the therapeutic range. In contrast, a third report showed no differences in Vd or CrCl after a 2.85-mg/kg dose (Hollenstein 2001). The resultant AUC was therefore significantly higher ( $6.18 \pm 1.7$  vs.  $3.02 \pm 0.95$  mg hour/L,  $p < 0.05$ ). Given the limited amount of data and the variability noted, caution is warranted with doses outside the recommended range when used in the absence of therapeutic drug monitoring.

### Vancomycin

Vancomycin dosing in obesity is challenging, secondary to the many factors that influence clearance beyond size and CrCl. Furthermore, using trough values versus AUC can lead to multiple AUC values for a given trough, depending on the dosing frequency used (Nix 2020). Loading doses of vancomycin are recommended for critically ill patients, and these are largely influenced by Vd. Pharmacokinetic studies indicate that vancomycin Vd increases with weight, but this increase is not proportional. In one study, vancomycin Vd was 52 L in a cohort of patients with morbid obesity (mean weight 165 kg) compared with 46 L in those with normal weight (mean weight 68 kg) (Bauer 1998). Similarly, a second study evaluated vancomycin Vd in patients with class III obesity (mean weight 144 kg) and reported that Vd does not scale proportionally with TBW (Dunn 2019). In fact, the calculated Vd was 0.52 L/kg, which is substantially lower than the standard empiric estimated Vd of 0.7 L/kg. Recent consensus guidelines recommend vancomycin loading doses of 20–25 mg/kg on the basis of TBW for patients with obesity, with a maximum dose (i.e., dose-capping strategy) of 3000 mg (Rybak 2020).

Other studies have evaluated vancomycin maintenance doses in obesity. Maintenance doses are largely influenced by clearance, and a strong correlation exists between clearance and weight ( $r = 0.948$ ,  $p < 0.001$ ) (Bauer 1998). However, several studies have described lower weight-based dosing in patients with obesity than in their non-obese counterparts (Crass 2018; Lin 2016; Morrill 2015; Reynolds 2012). One retrospective study reported that the most common daily dosage for patients with obesity (BMI 40 kg/m<sup>2</sup> or greater) who achieved target trough concentrations of 15–20 mg/L was 2000 mg (range 1000–3000 mg/day) (Morrill 2015). This is markedly lower than what might be expected using the weight-based doses recommended in non-obese patients (i.e., 15–20 mg/kg/dose given every 8–12 hours). In fact, the odds of target trough attainment were highly associated with vancomycin doses of 20–25 mg/kg/day using TBW (OR [95% CI] = 6.07 [1.01–36.51]). A second study described the effect of two dosing protocols on target trough attainment (10–20 mcg/mL) (Reynolds 2012). The original protocol used the consensus panel-recommended dose (15–20 mg/kg every 8–12 hours),

whereas the revised protocol used a somewhat lower dose (10 mg/kg every 12 hours). Compared with the original protocol, the revised protocol led to a higher frequency of target troughs (59% vs. 36%,  $p = 0.006$ ) and a lower frequency of supratherapeutic values (18% vs. 55%,  $p < 0.001$ ). Supratherapeutic troughs were more profound in the ICU cohort that was dosed using the original protocol whereby 79% had troughs exceeding 20 mcg/mL. A third study described vancomycin dose requirements using a continuous infusion in an obese versus non-obese surgical ICU population (Lin 2016). In patients with preserved renal function, the mean daily dose (not indexed by weight) required to achieve a target concentration of 20 mg/L was similar for patients with obesity and those without obesity ( $3676 \pm 1131$  vs.  $3882 \pm 674$  mg,  $p = 0.523$ ). Finally, one study developed an AUC-based nomogram using a clearance formula with allometric scaling for weight (Crass 2018). In this model, clearance equaled 9.656 minus 0.078 (age) minus 2.009 (SCr) plus 1.09 (sex: 1 if male, 0 if female) plus 0.04 (TBW)<sup>0.75</sup>. According to the nomogram, maintenance doses (based on clearance) could be 500–4500 mg/day and have a high probability of achieving an AUC of 400 or greater and a low probability of achieving supratherapeutic values (AUC 700 or greater). Considering a hypothetical 45-year-old male patient who weighs 150 kg with an SCr of 1 mg/dL, the resulting vancomycin dose using this strategy would be a loading dose of 2500 mg followed by 1750 mg every 12 hours (about 23 mg/kg/day).

### Daptomycin

Package labeling recommendations state that TBW should be used for daptomycin dosing, which is based on a small pharmacokinetic study showing greater clearance and AUC values in obese subjects than in non-obese subjects. However, these differences do not represent a proportional increase, which could lead to supratherapeutic concentrations in patients with obesity if TBW were used. For example, one study reported a higher maximum concentration ( $67.3 \pm 12.3$  mg/L vs.  $42.3 \pm 11.9$  mg/L,  $p = 0.029$ ) and AUC ( $494 \pm 62$  vs.  $307 \pm 54$ ,  $p = 0.002$ ) in patients with morbid obesity after a 4-mg/kg dose that was based on TBW (Pai 2007). Daptomycin has concentration-dependent activity, and higher doses have been associated with improved outcomes (Britt 2017). However, adverse effects may be more prevalent, particularly when minimum concentrations exceed 24.3 mg/L (Bhavnani 2010).

Alternative dosing strategies for daptomycin have been proposed. Smaller, retrospective studies have shown no difference in clinical outcomes between TBW-based and non-TBW-based (i.e., AdjBW, IBW) dosing regimens (Fox 2019; Ng 2014). Adjusted body weight using a correction factor of 0.4 was suggested in a comprehensive review (Meng 2017). One study described a fixed dosing strategy using Monte Carlo simulation in which a 500-mg dose yielded similar AUC values in both obese and non-obese individuals ( $638 \pm 144$  vs.  $658 \pm 94$ ) (Butterfield-Cowper 2018). Higher doses

(i.e., 750 mg) may be required in patients with severe infections such as septic shock. Clinical outcomes have not yet been evaluated with fixed, non-weight-based dosing. Collectively, these data indicate that daptomycin dosing using AdjBW is preferred.

### Linezolid

Data analyses evaluating linezolid dosing in obesity are limited. One pharmacokinetic study reported no association between TBW and AUC exposure and suggested standard dosing (i.e., 600 mg twice daily) for patients weighing up to 150 kg (Bhalodi 2013). A second study reported that linezolid trough concentrations were not associated with weight but that estimated CrCl calculated using the [Chronic Kidney Disease Epidemiology Collaboration \(CKD-EPI\) formula](#) was a significant covariate (Cojutti 2018). In fact, a Monte Carlo simulation analysis identified suboptimal exposure after standard 600-mg twice-daily dosing in some patients, depending on the estimated CrCl (using CKD-EPI) and organism MIC. A dosing nomogram was constructed that included maximum doses of 450 mg every 8 hours for some patients, especially when the CrCl exceeded 130 mL/minute. Escalation of doses to 600 mg every 8 hours was not recommended because of the high risk of overexposure and potential for serious adverse reactions (e.g., thrombocytopenia). In the absence of therapeutic drug monitoring, doses in this range should be avoided. Further studies evaluating alternative approaches are required, particularly with infections that have higher MIC values.

## OLDER ADULTS

About 16% of the U.S. population is 65 and older, which is expected to increase to 20% by 2030 and 23% by 2060 (U.S. Census Bureau 2017). Furthermore, it is estimated that by 2034, for the first time in U.S. history, older people (65 and older) will outnumber children (younger than 18 years). This greatly affects health care clinicians, given the many challenges this population presents, including the role of drug therapy. One particular problem is related to polypharmacy. Polypharmacy refers to the practice of prescribing multiple medications to an individual patient and is usually characterized by the use of five or more medications. One report cited an increase in the percentage of individuals prescribed five or more prescription medications from 24% in 1999 to 39% in 2012 (Kantor 2015). Another study reported that the average number of medications prescribed within the year before ICU admission was 13 (Bell 2011). These medications should be properly reconciled because unintentional discontinuation is more common in the ICU, which can lead to patient harm. However, just as important is careful evaluation for prescribing cascades (prescribing a new medication to treat the adverse effect of another).

Several other factors also complicate pharmacotherapy in critically ill older adult patients. Critically ill patients receive more than 30 different medications throughout their ICU stay, which increases the likelihood of adverse events or drug interactions (Cullen 1997). In fact, the risk of harm associated with medication errors and adverse drug events is about 2–3 times higher in ICU patients than in non-ICU patients

### Patient Care Scenario

A 69-year-old man (height 67 inches, weight 130 kg) is admitted to the ICU after a motor vehicle collision in which he sustained a pelvic fracture and multiple rib fractures. His SCr is 1.1 mg/dL, and his blood pressure and heart rate are 150/79 mm Hg and 110 beats/minute. He is not

mechanically ventilated, and his  $SaO_2$  values are 94%. On physical examination, he states that his pain is 9/10. What would you recommend for initial pain control and VTE prophylaxis?

### ANSWER

This patient presents after a motor vehicle collision in which he had multiple orthopedic trauma, placing him at very high risk of a VTE. His BMI is 45 kg/m<sup>2</sup>, which is categorized as class III obesity. The preferred medication for VTE prophylaxis is low-molecular-weight heparin because of its superior efficacy in this population. However, the pharmacokinetic alterations that exist because of obesity necessitate a dosing adjustment. Most data analyses describing low-molecular-weight heparin dosing in this population rely on anti-Xa concentrations, which indicate that a higher-than-standard dose is necessary. One study

reported a lower incidence of VTE in bariatric surgery patients using an enoxaparin dose of 40 mg twice daily. This patient's weight is consistent with that included in this study. Enoxaparin 40 mg twice daily is therefore an appropriate dose. For pain control, an intravenous opioid would be preferred, given his pain score and need for a rapid-acting agent. Although several options exist, hydromorphone would be preferred because it does not have an active metabolite that could possibly accumulate. Hydromorphone doses do not require adjustment for obesity; therefore, standard doses can be used.

1. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low-molecular-weight-heparin in bariatric surgery. *Obes Surg* 2002;12:19-24.
2. Nightingale CE, Margaron MP, Shearer E, et al. Peri-operative management of the obese surgical patient 2015. Association of Anaesthetists of Great Britain and Ireland Society for Obesity and Bariatric Anaesthesia. *Anaesthesia* 2015;70:859-76.

(Kane-Gill 2017). This is further complicated by the increased number of comorbidities in critically ill older adult patients for whom drug therapy may be indicated. Another factor is the variability between chronological age and physiologic age (Soto-Perez-de-Celis 2018). Recent data analyses have shown that this relationship is not linear and that chronological age is a poor marker of the health impact of aging (Lowsky 2014). Thus, age should not be used alone to determine overall health status. Finally, factors specific to the ICU make extrapolating data from the non-ICU setting difficult. Critical illness–associated acute organ dysfunction affects virtually every aspect of drug pharmacokinetics, with the potential to increase adverse effects. Prioritization of goals in the ICU are different and often change, leading to variance in the duration of drug exposure. In addition, use of medications for off-label indications is high and may be associated with adverse effects. Specifically, in one study, adverse drug effects increased by 8% for each additional off-label medication received (Smithburger 2015).

The American Geriatrics Society Beers Criteria are an explicit list of potentially inappropriate medications (PIMs) that should be avoided in patients 65 and older (AGS 2019). Many of these medications are commonly used in ICU patients. In many cases, these agents can easily be avoided (e.g., antihistamines with strong anticholinergic properties), but in other cases, their use may be unavoidable (e.g., amiodarone for atrial fibrillation, proton pump inhibitors [PPIs] for acute upper GI bleeding, NSAIDs for opioid minimization). Regardless, careful attention is required to ensure appropriate discontinuation upon discharge. Factors associated with the use of PIMs upon discharge are the number of preadmission PIMs, discharge to somewhere other than home, and discharge from a surgical (vs. medical) service (Morandi 2013).

## Pharmacokinetic Considerations

### Absorption

Several age-related changes in the GI tract can affect drug absorption. These include decreased splanchnic blood flow, decreased gastric emptying time, decreased GI motility, decreased gastric secretion, and decreased intestinal absorption surface. Despite these changes, the overall effect appears to be clinically insignificant (Klotz 2009). Factors to consider in the critically ill population for whom these alterations may be important include the fact that many older adult patients receive medications administered through a nasogastric tube, which is then clamped (i.e., removed from wall suction). Decreased gastric emptying time can increase the time for transit into the small intestine. If the drug has not emptied into the small intestine before nasogastric suction is reestablished, it will be removed and not absorbed. Next, the decrease in GI motility can lead to delayed onset for a medication that is significant when a rapid effect is desired

(e.g., an oral opioid for acute pain control). Finally, aging is associated with reduced first-pass metabolism because of decreased liver mass and perfusion. Bioavailability of drugs that undergo extensive presystemic elimination (e.g., propranolol, labetalol) will be increased (Shi 2011).

### Distribution

Aging is associated with significant changes in body composition that influence drug Vd (i.e., fat content increases by 20%–40%, and total body water decreases by 10%–15%) (McLean 2004). This increases the Vd for lipophilic drugs such as diazepam while decreasing the Vd for hydrophilic drugs (e.g., aminoglycosides and digoxin). Together with changes in body composition, minor changes occur in plasma protein binding. The extent of these changes, though, is more related to critical illness than to age. Acidic drugs (e.g., phenytoin, warfarin) are predominantly bound to albumin, which is typically decreased in patients with burns, liver disease, sepsis, uremia, and trauma. Free fractions are expected to be higher. However, basic drugs (e.g., morphine) bind to  $\alpha_1$ -acid glycoprotein, which is increased in patients with renal failure, burns, infections, and myocardial infarction and in those who have recently undergone surgery.

### Metabolism

Drug metabolism is largely influenced by hepatic blood flow and the liver's ability to extract the medication from the bloodstream. Aging is associated with a reduction in hepatic blood flow by about 40% (McLean 2004). Drugs that depend on hepatic blood flow (i.e., high-extraction drugs) such as morphine, labetalol, and verapamil may have reduced clearance. Drugs that depend on enzymatic function for clearance (as opposed to hepatic blood flow) are considered low extraction drugs and undergo either phase I reactions (i.e., oxidation, reduction, hydrolysis) or phase II reactions (glucuronidation, acetylation, sulfation). Phase I reactions are much more sensitive to age, and the clearance of drugs that are metabolized through these mechanisms may be reduced (e.g. diazepam, midazolam). By contrast, phase II reactions are not substantially impaired in older adults, and clearance of these agents is not reduced in an age-dependent fashion (McLean 2004).

The most important enzymatic pathway for phase I metabolism is through the CYP system. The efficiency of this system is affected by both patient age and critical illness. However, not all CYP isoforms are equally affected by increasing patient age. Moreover, although wide variability has been noted, clearance appears to be lower for substrates of CYP1A2 and CYP2C19, decreased or unchanged for substrates of CYP3A4 and CYP2C9, and unchanged for substrates of CYP2D6 (Cusack 2004).

### Elimination

Increased age is associated with several structural and functional changes within the kidney that affect drug clearance. A

substantial decline in renal mass occurs that is proportional to the decline in functioning glomeruli (Muhlberg 1999). Renal blood flow decreases by up to 10% per decade of life, starting at age 40. In fact, most individuals have a linear decline in glomerular filtration by about 0.75 mL/minute/year (Muhlberg 1999). Wide variability is noted with these changes, which are confounded by increasing comorbidities that become more prominent with advanced age.

The most common method for estimating kidney function for drug dosing is the Cockcroft-Gault equation. However, the equation is prone to error in older adults because of its reliance on SCr. Serum creatinine is influenced by body muscle mass, which is typically diminished in older adult patients. This leads to overestimation of CrCl. Similarly, relying on SCr alone is not appropriate because one study reported concealed renal insufficiency (i.e., renal insufficiency despite a normal SCr concentration) in 14% of hospitalized older adult patients (Corsonello 2005). To correct for the inherent overestimation of CrCl with the Cockcroft-Gault formula, some institutions round low SCr values to an arbitrary value of 1 mg/dL. However, this practice has not been shown to improve accuracy or bias and may lead to underestimating the CrCl (Winter 2012). Because of the risk of underdosing and the importance of aggressive therapy in critically ill patients, this practice should be avoided.

### General Dosing Principles

When crafting dosing regimens in older adult patients, clinicians must consider many overarching principles. First, aging is associated with several pharmacodynamic changes that can alter the therapeutic response and lead to an adverse effect. These changes are related to altered receptor density, altered receptor affinity, signal transduction (i.e., ability of the cells to respond to receptor occupation), and homeostatic mechanisms. In most cases, these result in greater sensitivity to the pharmacologic effect of the medication. Second, older adult patients have a lower physiologic reserve with impaired adaptive mechanisms, making them more susceptible to complications and adverse drug effects. Drug-related hypotension is more prominent because of reduced baroreceptor activity and lower sensitivity to catecholamines. Increased sensitivity to CNS-active drugs occurs secondary to more rapid CNS penetration and increased receptor affinity (Bowie 2007). Dosing strategies using lower doses that can rapidly be titrated to effect are preferred. Third, end-organ dysfunction can lead to not only accumulation of the parent drug but also any active metabolites. For example, morphine has an active metabolite, morphine-6-glucuronide, which has pharmacologic activity and is not efficiently removed through hemodialysis. Midazolam has an active metabolite,  $\alpha$ -1 hydroxy midazolam, which can accumulate in renal insufficiency, leading to excess or prolonged sedation. Finally, extremes in body weight are common among older adult patients, including low body mass. Data analyses

describing drug dosing in patients with a low BMI are sparse. In most cases, either standard doses or doses on the lower end of the dosing range are appropriate. Caution is warranted with fixed doses of anticoagulant medications (e.g., low-molecular-weight heparin) because doses commonly used for prophylaxis may in fact achieve therapeutic anticoagulation levels.

## Pharmacotherapy-Specific Recommendations

### Sedatives

Aging is associated with significant changes in neurologic activity, including a loss in brain mass (about 20%), reduction in cerebral blood flow, slower conduction, and fewer synapses (Oskvig 1999). As such, oversedation remains a major concern when selecting a sedation regimen in the older adult population. Recent evidence-based guidelines suggest light sedation targets using a non-benzodiazepine-based strategy (Devlin 2018). Sedation intensity is independently associated, in an escalating manner, with mortality, delirium, and delayed time to extubation (Shehabi 2018). In fact, even a brief period spent in deep sedation can increase mortality, thereby supporting the use of wake-up assessments (Balzer 2015). Moreover, it appears that post-ICU adverse psychological effects (e.g., posttraumatic stress disorder) are not adversely affected when light levels of sedation are maintained (Devlin 2018). Light levels of sedation also help facilitate early physical and occupational therapy with respect to the ABCDEF bundle (assess, prevent, and manage pain; both spontaneous awakening and spontaneous breathing trials; choice of analgesia and sedation; delirium-assess, prevent, and manage; early mobility and exercise; family engagement and empowerment).

Propofol is a preferred sedative for mechanically ventilated patients because of its short half-life and reduced time to extubation compared with a benzodiazepine. However, considerable pharmacokinetic and pharmacodynamic alterations with propofol occur with aging, ultimately leading to a more pronounced effect. Propofol clearance decreases with age, more so in women than in men (Akhtar 2015). Other research has reported concentration values ( $EC_{50}$ ) for loss of consciousness of 2.35, 1.8, and 1.25 mcg/mL for subjects who were 20, 50, and 75 years of age, respectively (Schnider 1999). This reflects about a 30%–50% reduction in dosing requirements. Dexmedetomidine is a centrally acting  $\alpha_2$ -agonist that has sedative and analgesic properties but no effect on respiratory drive. Few data analyses describe the pharmacokinetic and pharmacodynamic variability associated with aging, but dexmedetomidine clearance may be prolonged with an increased context-sensitive half-time (Iriola 2012). Dosage reduction in older adults of about 33% has been proposed (Andres 2019). Finally, midazolam clearance is about 30% lower in older adults, likely because of age-related changes in hepatic function (Polasek 2013). Furthermore, the

active metabolite for midazolam,  $\alpha_1$ -hydroxy midazolam, can accumulate and contribute to the sedative effect. One study reported that a dose reduction of 75% would be required to produce a similar sedative effect (for an endoscopic procedure) in a 90-year-old patient compared with a 20-year-old patient (Bell 1987).

Consideration of adverse effects is important when selecting a sedation regimen in older adult ICU patients. Hypotension, which can occur with each of these sedatives, can be particularly troublesome, especially in patients who may be hypovolemic. Other key safety concerns with propofol are bradycardia, hypertriglyceridemia, and propofol-related infusion syndrome (PRIS). Propofol-related infusion syndrome can be particularly difficult to recognize, given that its symptoms are nonspecific and common in the typical ICU patient (e.g., metabolic acidosis, cardiovascular collapse, rhabdomyolysis, hypertriglyceridemia, renal failure). Although PRIS has generally been reported in patients receiving high doses of propofol for a prolonged period, one large study noted that the clinical manifestations of PRIS were observed within 3 days in most patients (Roberts 2009). One crossover study reported a reduction in catecholamine requirements when changing from propofol to dexmedetomidine in patients with septic shock, but bradycardia events may be higher (Morelli 2019). Dexmedetomidine-associated hypotension can be reduced by avoiding the bolus dose and extending the time between dose titrations (Gerlach 2009). Benzodiazepines are well-known risk factors for delirium and should be avoided, if possible. Excipients like propylene glycol are present in some medications (e.g., lorazepam) and may result in additional toxic effects.

### **Analgesics**

All critically ill patients have some degree of pain during their ICU admission; therefore, analgesic needs should be assessed routinely and around-the-clock. Pain management in this population is complex because of pharmacokinetic and pharmacodynamic alterations, various sources of pain, presence of chronic pain, individual perceptions of pain, and tolerance. End-organ dysfunction and accumulation of drug metabolites that are pharmacologically active can lead to persistent analgesia and adverse effects. Furthermore, age-related changes to receptor density, affinity, and binding can cause increased sensitivity (Akhtar 2015). In general, opioid doses in older adults should be reduced by about 25%–50%, with consideration of longer dosing intervals and avoidance of drugs with active metabolites (e.g., morphine).

Fentanyl is a synthetic opioid that is widely used in the ICU because of its short half-life and lower prevalence of hypotension and bronchospasm (compared with other opioids), and its clearance is not affected by renal dysfunction. Despite these advantages, dosing modifications are still required in older adults. One study showed a significant, negative correlation between age and dosing requirements on the basis

of electroencephalogram end points (Scott 1987). This was more related to pharmacodynamic alterations (vs. pharmacokinetic) because brain sensitivity to narcotics increases as age advances from 20 to 85 years. Fentanyl is also available as a patch; however, this method of administration should be avoided because of the delayed time to reach peak effect and the prolonged duration that exists once the patch is removed. Hydromorphone has pharmacokinetic parameters that are similar to morphine but does not have an active metabolite. This makes hydromorphone preferable in older adults and patients with renal insufficiency. Meperidine should be avoided for pain control because of accumulation of the active metabolite, normeperidine.

Nonopioid adjuncts are often recommended as part of a multimodal analgesic approach to reduce opioid requirements and minimize adverse effects. Some agents, however, may not be suitable in the older adult population or should be used with caution. Ketorolac is a highly effective NSAID in patients with orthopedic trauma but is associated with bleeding complications and acute kidney injury. This risk is further exacerbated by the presence of several comorbidities (e.g., diabetes) and in patients with hypovolemia (either secondary to their primary disease or drug induced). Tramadol is a weak opioid agonist and CNS reuptake inhibitor of norepinephrine and serotonin that has been linked to seizures, serotonin syndrome, and hypoglycemia. Gabapentinoids such as gabapentin and pregabalin are recommended in patients with neuropathic pain, but dose-dependent sedation may be problematic, particularly when used in combination with an opioid. In fact, research has shown an increase in opioid-related deaths with chronic use of both gabapentin and pregabalin when co-prescribed with an opioid (Gomes 2018, 2017). As a result, the FDA has implemented changes to the package labeling (FDA 2020). In summary, selection of opioid adjuncts must be individualized, with appropriate deprescribing when indicated.

### **Delirium**

Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness. Delirium is common in ICU patients, and age is an important underlying risk factor. In fact, the incidence of delirium may exceed 70% in ICU patients (Peterson 2006). Hypoactive delirium may be more prevalent than other subtypes; therefore, routine screening should be performed using a validated screening tool (e.g., Confusion Assessment Method for the ICU, ICU Delirium Screening Checklist).

Prevention of delirium should be the primary focus in the ICU because effective treatment methods are limited. Several risk factors exist for developing delirium, but few are considered modifiable. Benzodiazepine use is well documented as a risk factor for delirium. In a landmark study of 198

mechanically ventilated patients, lorazepam administration was identified as a significant risk factor for daily transition to delirium (OR [95% CI] = 1.2 [1.1–1.4]) (Pandharipande 2006). A second study also showed an increased risk of delirium with benzodiazepines, but this was more recognized with continuous infusions (Zaal 2015). Other medication-related risk factors that have been proposed include use of corticosteroids and anticholinergic medications, but currently available data analyses remain inconclusive (Devlin 2018). Nevertheless, clinicians should continue to weigh the risk-benefit with such therapies and ensure that the lowest effective dose is being prescribed with an appropriate therapy duration. Current evidence does not support the routine use of antipsychotics for the prevention of delirium (Oh 2019).

The role of pharmacotherapy for delirium is limited. Evidence-based guidelines do not support routine administration of haloperidol or an atypical antipsychotic for treatment (Devlin 2018). Short-term therapy with an antipsychotic can be considered in patients with significant distress secondary to delirium symptoms or in those with agitation who may be physically harmful to themselves or others. Low-dose antipsychotics (vs. sedatives) may play a role at night in patients with insomnia who do not respond to nonpharmacologic interventions, but more data analyses are needed. Dexmedetomidine may improve sleep in hemodynamically stable patients or facilitate extubation in patients with agitated delirium (Skrobik 2018; Reade 2016).

### **GI-Related Medications**

The prevalence of constipation increases with age, reaching rates of up to 45% in some reports (De Giorgio 2015). Rates are even higher in patients who reside in nursing homes, a population that often transitions back and forth from the ICU. A careful medication history is necessary because up to 74% of these patients report daily laxative use (Bouras 2009). Furthermore, GI-related adverse effects are common with many medications routinely used in the ICU (e.g., opioid analgesics). Bulking agents (e.g., psyllium), osmotic laxatives (e.g., PEG 3350), and stimulant laxatives (e.g., bisacodyl, senna) are recommended when constipation does occur (Wald 2016). Preemptive therapy is suggested in high-risk patients, such as those receiving scheduled opioids. Constipation in ICU patients has been linked to adverse clinical outcomes (Gacouin 2010).

Stress ulcer prophylaxis with acid-suppressive agents is widely used in the critical care setting, with PPIs most commonly selected (Barletta 2014). Proton pump inhibitors have been linked to infectious complications, including *Clostridioides difficile* diarrhea and pneumonia (Barletta 2016). One recent study reported increased mortality in ICU patients with a high severity of disease who received PPIs compared with placebo (Marker 2019). In addition, long-term PPI use has been associated with fractures, osteoporosis, dementia, and chronic kidney disease (Maes 2017). Although these adverse

effects are unlikely with short-term use in the ICU, many patients are inadvertently discharged on acid-suppressive therapy (Scales 2016). One study even reported an association between 1-year mortality and PPI use in older adult patients who were discharged from an acute care hospital. Stress ulcer prophylaxis should only be provided in patients who are considered at high risk of clinically important bleeding. Medications should be reconciled upon transitions in care to ensure the discontinuation of unnecessary therapies.

### **Anticoagulants**

The decision to administer an anticoagulant in the older adult population for either preventing or treating VTE is similar to that in non-older adult patients (i.e., a careful evaluation of risk-benefit with that particular medication). However, advanced age is associated with a significant increase in major bleeding, largely because of the pharmacokinetic variability that exists, the potential for drug accumulation, and the many comorbidities that exist, which also increase bleeding risk (e.g., renal failure). Clinicians must consider several factors when choosing an anticoagulant. Age-related declines in renal function may lead to drug accumulation and increased bleeding for the anticoagulants that are renally cleared (e.g., low-molecular-weight heparins, fondaparinux, dabigatran). Bleeding rates with low-molecular-weight heparin are higher when the CrCl is less than 30 mL/minute, and enoxaparin doses should be adjusted below this threshold (Lim 2006; Monreal 2006). Fondaparinux is contraindicated in patients with a CrCl less than 30 mL/minute or a TBW less than 50 kg.

Although not commonly used in the critical care setting, oral anticoagulants are also affected by advanced age. Older adults may be more sensitive to the effects of warfarin. The mechanism is multifactorial and may be related to hypoalbuminemia, malnourishment, or decreased dietary intake of vitamin K. In fact, one longitudinal study evaluating dosing requirements in patients stabilized on warfarin noted a 21% reduction in warfarin requirements over a 15-year period (Wynne 1996). Direct oral anticoagulants are widely considered for both preventing and treating VTE secondary to their improved safety profile (Rali 2019). In patients older than 75, however, both dabigatran and rivaroxaban have been associated with a greater risk of GI bleeding than warfarin (Romanelli 2016; Abraham 2015). Apixaban or edoxaban may be preferred. Furthermore, dabigatran capsules cannot be opened; thus, administration may be difficult in patients who cannot swallow.

A final concern is the availability of an antidote if rapid anticoagulation reversal is required. Guidelines suggest 4-factor prothrombin complex concentrates for the reversal of warfarin (Frontera 2016). Idarucizumab rapidly and completely reverses dabigatran (Pollack 2017). Although this finding was not exclusive to older adults, the median age was 77 years (range 48–93), and only 13% had a CrCl of 30 mL/minute or less. However, failure was reported in one case series of

two patients, largely because of massively supratherapeutic dabigatran concentrations (Steele 2018). Finally, andexanet alfa is approved for reversal of rivaroxaban and apixaban. However, the high acquisition cost, lack of high-quality post-marketing experiences, and limited availability of andexanet alfa may be problematic.

### Antimicrobials

Around 50% of hospitalized patients receive at least one dose of an antimicrobial, and antimicrobial use is higher in both older adults and the critically ill population (Magill 2014). Older adult patients have several characteristics that warrant dosage adjustment (e.g., end-organ dysfunction, decreased clearance, decreased Vd), but careful evaluation is necessary to ensure that pharmacodynamic goals are met. For example, a higher  $t > MIC$  was associated with improved clinical outcomes in one study evaluating  $\beta$ -lactam therapy in critically ill patients (100%  $t > MIC$ , OR [95% CI] = 1.56 [1.15–2.13] vs. 50%  $t > MIC$ , OR [95% CI] = 1.02 [1.01–1.04]) (Roberts 2014). In a second study, vancomycin doses that did not reach the goal AUC/MIC targets on day 1 were associated with an increased risk of clinical failure (Lodise 2014).

Many studies have highlighted the challenges with drug dosing in the ICU and the potential for standard doses of antimicrobials to be insufficient (Roberts 2014; Taccone 2010). In contrast, adverse drug events are more prominent in older adults, which creates the need for individualization of therapy with careful assessment of risk-benefit. When applicable,

### Practice Points

- When dosing medications in critically ill patients with obesity, seek consistency among clinicians involved in size descriptor estimates and measurements.
- There is increased variability with pharmacokinetic parameters such as Vd and clearance in critically ill patients compared with non-critically ill patients. Use caution when extrapolating conclusions from studies that were conducted outside the ICU setting.
- The duration of effect for a single or isolated dose of a lipophilic drug is more dependent on Vd than on clearance.
- Most drugs used in the ICU that are renally cleared do not have properties of dose proportionality.
- The risks of administering a large dose of a medication must always be considered, despite the presence of pharmacokinetic data showing dose proportionality. In many instances, administration of smaller doses that can be titrated to effect are preferred.
- Both pharmacokinetic and pharmacodynamic alterations exist in older adult patients that can increase the risk of an adverse effect.
- Many medications used in the ICU have active metabolites that can accumulate with end-organ dysfunction. These metabolites contribute to the overall pharmacologic effect and can lead to adverse effects.
- Avoid polypharmacy and prescribing cascades in older adults.

drugs with a favorable safety profile should be prioritized over those with a narrow therapeutic window. End-organ function should be assessed accordingly. The decision to lower doses on the basis of renal insufficiency must include the risks associated with underdosing and the potential for treatment failure, particularly when renal insufficiency may be transient. One study reported that more than one-half of patients who presented to the hospital with infections and acute kidney injury on admission had resolution of acute kidney injury within 48 hours (Crass 2019). Because early appropriate therapy significantly determines outcomes in critically ill patients, unnecessary dosage adjustment can contribute to treatment failure. This is particularly true in patients with septic shock when the Vd is larger (because of critical illness), and higher initial doses (i.e., loading doses) may be required. Deferred renal dose adjustment should be considered when dealing with medications that are generally considered safe (e.g., penicillins, cephalosporins). In all cases, therapeutic drug monitoring should be used as indicated.

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# Self-Assessment Questions

1. A newly approved antimicrobial requires weight-based dosing. Pharmacokinetic studies show that volume of distribution (Vd) and CrCl correlate best with fat-free mass. Which one of the following size descriptors would be best to use when dosing this medication for a patient whose height is 70 inches and whose weight is 130 kg?
  - A. Adjusted body weight (AdjBW) using a correction factor of 0.6
  - B. Ideal body weight (IDW)
  - C. Lean body weight (LBW)
  - D. Total body weight (TBW)
2. You are reviewing a proposal for an internal dosing guideline for drug dosing in patients with obesity. This guideline has a table that describes the pharmacokinetic alterations that occur with obesity. Which one of the following best describes an example where the properties of dose proportionality exist and weight-based dosing using TBW can be considered?

Patient	Weight (kg)	Volume of Distribution (L)	Creatinine Clearance (mL/min)
A	70	35	60
	100	40	65
B	80	32	100
	140	56	175
C	75	70	80
	150	100	120
D	65	16	90
	120	30	120

- A. Patient A
  - B. Patient B
  - C. Patient C
  - D. Patient D
3. You must calculate a loading dose for a new sepsis drug in a patient weighing 150 kg with pneumonia and septic shock. The patient has mild renal insufficiency with an estimated CrCl of 30 mL/minute. Which one of the following is most important to consider for this patient?
    - A. Loading doses for medications with a small Vd should be administered using LBW as the weight metric for calculations.
    - B. Loading doses for medications with a large Vd should be avoided because of concerns for adverse reactions.
    - C. Loading doses listed in the package labeling would be appropriate.
    - D. Loading doses should be reduced in patients with compromised drug clearance.

4. A patient with extreme obesity (weight 160 kg) is admitted to the ICU with respiratory failure requiring mechanical ventilation. Which one of the following sedation strategies is best to recommend for this patient?
  - A. Dexmedetomidine 160-mcg bolus, followed by 0.2 mcg/kg/hour on the basis of AdjBW
  - B. Dexmedetomidine 0.2 mcg/kg/hour on the basis of AdjBW
  - C. Midazolam 0.05-mg/kg/hour infusion on the basis of TBW
  - D. Propofol 5 mcg/kg/minute on the basis of TBW
5. A patient with extreme obesity (weight 130 kg) presents to the ICU with septic shock secondary to an intra-abdominal infection. Fluid resuscitation with lactated Ringer solution is initiated, and broad-spectrum antimicrobials are administered. Urinary output is around 10–15 mL/hour, and mean arterial pressure (MAP) is 55–60 mm Hg. Serum lactate is 5 mmol/L. The team wants to initiate norepinephrine with the addition of vasopressin if norepinephrine is ineffective. Which one of the following is best to recommend for this patient's vasopressor dosing?
  - A. Non-weight-based dosing of norepinephrine and non-weight-based dosing of vasopressin
  - B. Non-weight-based dosing of norepinephrine and weight-based dosing of vasopressin
  - C. Weight-based dosing of norepinephrine (using TBW) and non-weight-based dosing of vasopressin
  - D. Weight-based dosing of norepinephrine (using TBW) and weight-based dosing of vasopressin (using TBW)
6. A 32-year-old man (weight 175 kg; BMI 62 kg/m<sup>2</sup>) is in the surgical ICU after a motorcycle collision in which he had fractures to his ribs, acetabulum, tibia, and fibula. He is mechanically ventilated but not requiring vasopressor support (blood pressure is 142/83 mm Hg). There are no concerns for renal insufficiency because his SCr is 0.9 mg/dL and urinary output is appropriate. Which one of the following enoxaparin dosages is best to recommend for preventing venous thromboembolism (VTE) in this patient?
  - A. 30 mg twice daily
  - B. 40 mg twice daily
  - C. 70 mg twice daily
  - D. 90 mg daily
7. A 56-year-old man is admitted to the medical ICU after a rapid response code was called for hypoxia, shortness of breath, and chest pain. He is later given a diagnosis

of a pulmonary embolism. The team would like to use low-molecular-weight heparin for treatment. Which one of the following best summarizes the collective body of literature?

- A. Bleeding rates in patients with extreme obesity are similar to those in non-obese patients.
  - B. Dose-capping strategies are not widely used in studies describing low-molecular-weight heparin dosing in obesity.
  - C. Patients with weights in excess of 150 kg are well represented in both pharmacokinetic and clinical trials.
  - D. Therapeutic anti-Xa concentrations are generally obtained with doses that are less than the standard 1-mg/kg dose according to TBW in patients with obesity.
8. A 29-year-old man (height 58 inches, weight 125 kg) is admitted to the ICU with a traumatic brain injury. On hospital day 5, he develops a fever and leukocytosis with a new infiltrate on chest radiography suggesting pneumonia. His SCr is 0.8 mg/dL. He has not been exposed to other antibiotics. Which one of the following gram-negative antibiotic regimens is best to recommend for this patient?
- A. Cefepime 2 g twice daily administered over 30 minutes
  - B. Levofloxacin 750 mg daily administered over 90 minutes
  - C. Meropenem 1 g every 8 hours administered over 3 hours
  - D. Piperacillin/tazobactam 3.375 g every 8 hours administered over 4 hours
9. A 64-year-old woman (height 55 inches, weight 145 kg) presents to the ICU with respiratory failure and sepsis. Her SCr is 1.0 mg/dL. The team would like to begin empiric broad-spectrum antimicrobial therapy that includes vancomycin. Your institution has a protocol for vancomycin dosing. Which one of the following principles pertaining to vancomycin dosing in obesity is most important to consider for this patient?
- A. A continuous infusion of 30 mg/kg according to TBW is more likely to yield the target AUC.
  - B. Extrapolation of protocols developed for non-obese patients may lead to overdosing.
  - C. The expected Vd would be 0.7 L/kg.
  - D. The loading dose of 25–30 mg/kg calculated using TBW should be administered.
10. An 82-year-old woman with a medical history significant for diabetes, coronary artery disease, and hypertension is admitted to the ICU with an acute exacerbation of chronic obstructive pulmonary disease. You try to reconcile her home medications. Which one of the following examples best describes a potential prescribing cascade?
- A. Albuterol, azithromycin, aspirin
  - B. Amlodipine, furosemide, oxybutynin
  - C. Furosemide, lisinopril, spironolactone
  - D. Metformin, metoprolol, simvastatin
11. An 89-year-old man is admitted to the surgical ICU after a ground-level fall in which he hit his head and had a traumatic brain injury. His medical history is significant for hypertension, gastroesophageal reflux disease, and chronic back pain. He is mechanically ventilated and has a nasogastric tube for GI access. He is receiving continuous enteral nutrition. The team would like to begin enteral drug administration. The team would like to begin enteral drug administration through the nasogastric tube. For which one of the following scenarios would an age-related change in absorption be most concerning in this patient?
- A. Nasogastric administration of metoclopramide
  - B. Nasogastric administration of labetalol
  - C. Nasogastric administration of lansoprazole
  - D. Nasogastric administration of phenytoin
12. An 89-year-old woman (height 62 inches, weight 52 kg) presents to the ICU with cholangitis. Her SCr is 0.5 mg/dL. Fluid resuscitation is initiated, and piperacillin/tazobactam is initiated empirically. Which one of the following is the best estimated CrCl to use when dosing piperacillin/tazobactam for this patient?
- A. 30 mL/minute
  - B. 40 mL/minute
  - C. 60 mL/minute
  - D. 80 mL/minute
13. A 77-year-old woman presents to the ICU with a chronic obstructive pulmonary disease exacerbation. She is intubated secondary to respiratory failure and will require sedation. Her blood pressure and heart rate are 110/68 mm Hg and 58 beats/minute. Which one of the following is best to recommend for this patient?
- A. Dexmedetomidine 1-mcg/kg bolus followed by a 0.2-mcg/kg/hour infusion
  - B. Lorazepam 1 mg every 4 hours
  - C. Midazolam 2-mg/hour infusion
  - D. Propofol 5 mcg/kg/minute
14. A 90-year-old man is admitted to the ICU after a ground-level fall in which he had a hip fracture. His medical history is significant for hypertension, diabetes, and chronic pain, for which he takes oxycodone regularly. Currently, he is mechanically ventilated and receiving fentanyl 25 mcg/hour, propofol 35 mcg/kg/minute, and

quetiapine 50 mg twice daily. On physical examination, he appears agitated with an ICU Delirium Screening Checklist score of 5, Richmond Agitation-Sedation Scale score of -2, and Critical-Care Pain Observation Tool score of 2. His blood pressure is 130/80 mm Hg, heart rate is 84 beats/minute, QTc on ECG is 492, and SCr is 0.7 mg/dL. Which one of the following is best to recommend for this patient?

- A. Add lorazepam 2 mg as needed for agitation.
- B. Change propofol to dexmedetomidine.
- C. Change quetiapine to intravenous haloperidol.
- D. Discontinue fentanyl.

15. An 85-year-old man is in the ICU after a hemicolectomy secondary abdominal sepsis caused by a large bowel perforation. His hospital stay is complicated by a deep vein thrombosis, for which he is receiving a heparin infusion. He is tolerating enteral nutrition, which is being delivered through a nasogastric tube. His SCr is 1.3 mg/dL. His other medications include oxycodone, simvastatin, metoprolol, insulin, pantoprazole, metoclopramide, cefepime, and metronidazole. The team would like to transition his anticoagulation to oral therapy. Which one of the following is best to recommend for this patient?

- A. Apixaban
- B. Dabigatran
- C. Rivaroxaban
- D. Warfarin