MINIREVIEWS

Designing drug regimens for special intensive care unit populations

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Abstract

This review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions. The data sources included a literature search of MEDLINE and EMBASE with reviews of reference lists of retrieved articles. Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy. Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients were extracted. Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses. Critically ill patients with changes in body size, habitus and composition require special consideration when designing medication regimens, but there is a paucity of literature on which to make drug-specific, high-level evidence-based recommendations. Based on the evidence that is available, general recommendations are provided for drug choice or dosing in special critically ill populations.

Key words: Drug dosage calculations; Pharmacokinetics; Critical care; Body composition; Obesity; Pregnancy

Core tip: Special populations of intensive care units patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

INTRODUCTION

What are special populations?

The term "special populations" does not have a uniform definition. For example, within the National Institutes of Health (NIH) there is an Office for Special Populations within the National Institute of Mental Health (http://www.nimh.nih.gov/about/organization/od/office-for-special-populations-osp.shtml) that refers to "the mental health needs of women and minority populations". On the other hand, there is an Office of Special Populations within the National Institute on Aging (http://www.nia.nih.gov/about/offices/office-special-populations) refers to "older women, minorities, and persons with disabilities" and the National Institute on Alcohol Abuse and Alcoholism (http://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders) that refers to "Special populations are groups who face particular risks from drinking alcohol based on personal characteristics such as age or gender". The overarching theme to these definitions is that they try to focus on the special populations of particular importance to each institute. Along those lines, this review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions.

LITERATURE STUDY

Data sources

Searches of MEDLINE and EMBASE were performed. The search strategies were developed in cooperation with a medical librarian with training in the performance of systematic reviews. The initial search strategy for MEDLINE was: (((((("critical care" (MeSH Major Topic) or "critically ill patients" or "critically ill" or "critical patients" or "critical patient") and (((("physiological phenomena" (MeSH Terms)) or "body composition" (MeSH Terms) or "body size descriptors" or "body weight changes" or "body weight change" or "body size" or "body composition" or "physical body change" or "body change"))) and English (lang))))). For EMBASE the initial search strategy was: "intensive care"/exp or "critical care": ab,ti or "critically ill patients": ab,ti or "critically ill":ab,ti or "critical ill":ab,ti or "critical patient":ab,ti and ("body weight"/exp or "weight change"/exp or "weight fluctuation"/exp or "weight, mass and size"/exp or "body composition"/exp or "body weight change":ab,ti or "body weight changes":ab,ti or "body size":ab,ti or "body composition":ab,ti or "physical body change":ab,ti) and (English)/lim and [(embase)/lim or (embase classic)/lim]. Subsequent searches were performed looking at more specific special populations. For example for MEDLINE: ((("critical care" (MeSH Terms) or "critically ill patients" or "critically ill" or "critical patients" or "critical patient") and ("body composition" (MeSH Terms) or "body size descriptors" or "body weight changes" or "body weight change" or "body size" or "body composition" or "physical body change" or "body change" or "Overweight" (Mesh) or "Obesity" (Mesh) or "overweight" or "obese" or "obesity" or "Thinness" (Mesh) or "underweight" or "Amputation Stumps" (Mesh) or "short limbs" or "missing limbs" or "Pregnant Women" (Mesh) or "Pregnancy" (Mesh) or "pregnant patients" or "pregnant women" or "Extracorporeal Membrane Oxygenation" (Mesh) or "Plasma Exchange" (Mesh))) and ("Treatment Outcome" (Mesh) or "Pharmaceutical Preparations" (Mesh) or "medication regimen" or "medication regimens" or "Patient Care Planning" (Mesh) or "Patient Care Management"(Mesh) or "Therapeutics" (Mesh) or "Drug Therapy" (Mesh) or "Drug Delivery Systems" (Mesh))).

Study selection

Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation (ECMO) or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy.

Data extraction

Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients.

Data synthesis and analysis

Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses (Table 1). For this reason, it was decided to focus this review on general principles related to drug choice or dosing in special populations of critically ill patients, rather than trying to provide specific dosing recommendations for every medication that might be used in the intensive care units (ICU) setting[1]. Selected medications will be discussed to provide examples of dosing issues, but most of the references will list review articles and guidelines of particular relevance to the special population under consideration. Recommendations that are provided are done so under the assumption that there are no concomitant therapies or co-morbidities that would alter the parameter of interest. It is also presumed that additional expertise, such as that of a clinical pharmacist, will be sought when dealing with these difficult therapeutic decisions.

This paper will be divided into 2 parts beginning in Part 1 with an overview of body composition and how various size descriptors such as body weight that are used for drug dosing reflect changes in body

Table 1 Results of search strategies for randomized controlled trials

	Number of citations
MEDLINE	
Initial search strategy as described in text	5316
Search strategy limited to "clinical trial" and "humans"	726
Of the 725 citations, the number of RCTs with clinically relevant endpoints	0
MEDLINE	
Focused search strategy as described in text	2586
Search strategy limited to "clinical trial" and "human"	176
Of the 176 citations, the number of RCTs with clinically relevant endpoints	0
EMBASE	
Initial search strategy as described in text limited to terms indexed as major focus	1898
Search strategy limited to "human" or "clinical trial"	1431
Search strategy limited to "article"	870
Of the 871 citations, the number of RCTs with clinically relevant endpoints	0

RCT: Randomized controlled trial.

Table 2 Changes in body composition during intensive care units stay that may affect drug disposition

Lean *vs* adipose tissue changes during more prolonged stay
  Loss of lean tissue
  Gain of adipose tissue
    Distribution of adipose tissue (*e.g.*, subcutaneous *vs* visceral)
Gains or losses of total body water throughout stay
Distribution of retained fluid (*e.g.*, intracellular *vs* extracellular, interstitial *vs* intravascular)

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Table 3 Weight descriptors commonly used in adult patients in the clinical setting

Ideal body weight (IBW)
  IBW in kg for men = 50 kg + 2.3 kg for each inch in height over 60 inches
  IBW in kg for women = 45.5 kg + 2.3 kg for each inch in height over 60 inches
Adjusted body weight (ABWadj)
  ABWadj in kg = IBW + 0.4 (actual weight - IBW)
Lean body weight (LBW)
  LBW (men) = $(1.10 \times$ weight in kg$) - \{120 \times [($weight in kg$)/($height in cm$)]^2\}$
  LBW (women) = $(1.07 \times$ weight in kg$) - \{148 \times [($weight in kg$)/($height in cm$)]^2\}$
Body mass index (BMI)
  BMI = actual body weight (ABW) in kg divided by (height in m)^2
Body surface area (BSA) in m^2
  BSA = square root [(height in cm × ABW in kg)/3600]

Various methods have been used for estimation - inclusion in this table should not be interpreted as support for a particular method. Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

composition. The remaining sections of Part 1 deal with pharmacokinetic and therapeutic drug monitoring considerations when selecting and dosing drugs in special populations. Part 2 of this paper will highlight specific populations with changes in body size, habitus and composition that require special consideration when designing drug regimens: obese patients, patients who are underweight, amputated or missing limbs, pregnant patients, and patients undergoing ECMO or plasma exchange.

PART 1

Body composition
Body size and shape (also known as habitus) refer to physical attributes of individuals such as height, weight, and body proportions. Anthropometry is the measure of such attributes. Epidemiological studies conducted in the United States have demonstrated not only an increase in attributes such as weight but also increased variability in anthropometric indicators with implications for drug dosing[2]. Table 2 lists body composition changes that frequently occur in critically ill patients during more prolonged ICU stays.

There are a number of techniques for assessing body composition that have been used to assess tissue differences such as fat *vs* fat-free mass, but have yet to receive widespread use in the clinical arena[3]. While much of this research has focused on the nutritional aspects of body composition measurements[4], the metabolic aspects of the measurements have implications for the pharmacokinetics and pharmacodynamics of medications[5]. Approximately 25% of weight gain or loss is fat free mass[6]. Further, different types of adipose

tissue have differing metabolic activity. Brown adipose tissue has been investigated as an anti-obesity tissue[7].

Size descriptors
Since sophisticated technologies for assessing body composition are not typically employed in the ICU setting, most prognostic and drug dosing information based on physical attributes is derived from basic size descriptor information such as height, weight, sex or some combination of these variables (see Table 3). In particular, body mass index has been studied as an indicator of morbidity and mortality in critically ill patients. The relationship between body mass index and mortality is not linear and there appears to be a so-called obesity paradox in which obese patients as defined by a BMI range between 30 and 39.9 kg/m^2 have a lower ICU mortality compared to patients of more extreme weights[8,9].

While commonly used to categorize and stratify patients by height and weight, body mass index is used less frequently as a size descriptor for drug dosing. The choice of size descriptor for drug dosing is between actual body weight or some type of adjusted

Table 4   Estimates and measurements of size descriptors such as height and weight
Strive for consistency and standardization within and between all healthcare professionals and staff involved in size descriptor estimates and measurements. Examples include: Method of estimates including formulas and equations used for calculations Instruments used for measurement and how utilized (*e.g.*, clothes off or on for weight recordings) Recording and use of units of estimates and measurements (*e.g.*, centimeters *vs* inches, pounds *vs* kilograms) Terminology related to size descriptors (*e.g.*, ideal weight, adjusted weight) Ensure proper communication and documentation of method (*e.g.*, patient *vs* provider, estimate *vs* measurement) used to obtain estimates and measurements of size descriptors Have ongoing education with evaluation of all personnel involved in the determination and documentation of estimates and measurements Have periodic evaluation of compliance by area (*e.g.*, ICU *vs* emergency department) Ensure that age-appropriate instruments are available and have regularly scheduled calibration Use technology (*e.g.*, automated infusion devices, dosing calculators) when available to reduce chance of medication errors

Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. ICU: Intensive care units.

Table 5   Pharmacokinetic considerations in the critically ill patient
Data from pharmacokinetic studies are no substitute for clinical monitoring of the individual patient's response to therapy Pharmacokinetic parameters derived from studies involving normal volunteers or less severely ill patients are not directly applicable to the critically ill patient Average parameters for volume of distribution and clearance are larger and have much greater variability in critically ill patients compared with less severely ill patients The duration of action of single or isolated IV doses of more lipophilic drugs used in the ICU is a function more of distribution than of clearance The values for volume of distribution and clearance frequently change from baseline with prolonged drug administration because of factors such as accumulation or altered elimination For drugs with active metabolites, the pharmacokinetics of the metabolites as well as the parent compound must be considered Drug absorption is important not only with oral or enteral administration but also with intramuscular and subcutaneous injections

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body weight. Clearly, there are implications for body composition differences on medications dosed based by body weight even when weight is appropriately measured[10]. Table 4 describes some of the more important issues to consider relative to size descriptor measurements.

Pharmacokinetic considerations and therapeutic drug monitoring

Volume of distribution is the pharmacokinetic parameter of most importance for giving loading doses of drugs and it is expected that more lipophilic drugs would have more extensive distribution. Lean body weight appears to be more predictive of renal clearance than actual body weight for obese patients, but there is substantial variation in clearance in critically ill patients[11,12]. Further, critically ill patients may have augmented measured creatinine clearance values[13].

An understanding of the concept of dose proportionality is important for deciding how to apply pharmacokinetic data from patients with near-normal body size and shape to patients with more extreme forms of size, shape and body composition. Basically, dose proportionality suggests that pharmacokinetic parameters change in the same direction and same degree as changes in body weight. Tables 5 and 6 describe important considerations when evaluating pharmacokinetic and dose proportionality issues in critically ill patients.

Because drug dosing based on pharmacokinetic parameters is often insufficient to accurately predict pharmacologic effects in individual patients, therapeutic drug monitoring may help to provide additional information about the body's handling of a drug. Unfortunately, in most clinical settings, only a limited number of drugs have assays for assessing concentrations of the drugs in the body; even when such assays are available, they do not always have a clear-cut correlation with the pharmacodynamic and pharmacological properties of a particular drug (Table 7). Importantly, this discussion of pharmacokinetics and therapeutic drug monitoring is based on generalizations and should not be used to guide dosing regimens of specific drugs. Instead, drug dosing regimens in patients of more extreme body compositions should be based on evidence from a variety of sources as exemplified by the approach used in Table 8 for obese patients.

PART 2

Drug dosing in obese patients

It is not surprising that epidemiological studies continue to track the prevalence and markers (*e.g.*, body mass index) of obesity and associated health outcomes. What is surprising is the relative lack of data on drug dosing in obesity, particularly in patients with more extreme forms of obesity[14]. Currently, there is no mandate that

Table 6 Assessment of possible dose proportionality in studies with obese subjects[1]

Did the study involve a comparator group of normal weight subjects of similar demographics (*e.g.*, age, height, gender) and co-morbidities as the obese subjects?

Did the values of pharmacokinetic parameters unadjusted for bodyweight (*e.g.*, volume of distribution in mL and clearance in mL/min) increase proportionally to weight in the obese *vs* the normal-weight subjects?

Were the values of pharmacokinetic parameters adjusted for actual bodyweight (*e.g.*, volume of distribution in mL/kg and clearance in mL/min per kilogram) similar in the obese and normal-weight subjects?

Did the values of pharmacokinetic parameters adjusted for ideal bodyweight (*e.g.*, volume of distribution in mL/kg and clearance in mL/min per kilogram) increase proportionally to weight in the obese *vs* the normal-weight subjects?

Was the calculated half-life based on the pharmacokinetic parameters similar in the obese and normal-weight subjects?

When actual bodyweight was used in weight-based dosing protocols were the therapeutic effects and dose-related adverse drug events similar in the obese and normal-weight subjects?

[1]If the answers to all of these questions are yes, the data suggests that dose proportionality is present, although this does not necessarily mean that actual bodyweight should be used in weight-based dosing protocols. Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Table 7 Considerations with therapeutic drug monitoring

Blood concentration measurements are not available for the majority of drugs used in critically ill patients

So-called therapeutic ranges for therapeutic drug monitoring (TDM) are typically derived from studies involving small numbers of patients

Most therapeutic ranges are based on steady-state drug concentrations, so non–steady-state concentrations can be very difficult to interpret (and often meaningless)

Disease states that affect a drug's volume of distribution or clearance often negate the presumption of steady-state conditions necessary for proper interpretation of concentrations

The minimum and maximum concentrations used to define a therapeutic range are often quite arbitrary and not necessarily applicable to a specific patient

The free or unbound form of a drug is the active form, but the total drug concentration is most commonly measured by clinical laboratories

Total drug concentrations for a drug with high protein binding (*e.g.*, > 90%) can be difficult to interpret when protein concentrations are decreased or when other drugs or diseases displace drug

Clinical response, not a TDM measurement, should be the primary driver of dosing decisions

The administration and timing of drug doses prior to TDM measurement should be verified, not presumed, because these affect the proper interpretation of the measurement

TDM is most useful when clinical indicators are misleading or not available or when the clinical indicator is a problem that the clinician is trying to prevent (*e.g.*, aminoglycoside nephrotoxicity)

Unnecessary TDM should be avoided (*e.g.*, ordering daily measurements of drug concentrations for a drug with a long half-life) because it may lead to inappropriate changes and unnecessary TDM costs

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product labeling provide information on drug dosing in obesity, or for that matter, what weight should be used for weight-based dosing of medications. Even the word "weight" as used in most product brochures is not defined, so an assumption is usually made by clinicians that the term is referring to actual body weight. For drugs that have non-weight-based dosing regimens (*e.g.,* mg per dose rather than mg/kg per dose), the clinician make elect to use the higher end of the dosing range for drugs with a rather wide therapeutic index. The issue becomes more complicated for weight-based dosing regimens in which the choice of weight is not clear.

When dosing an obese patient on a drug that does not include specific recommendations in the product labeling, the first step should be to perform a literature search looking for relevant investigations. The clinician may find that key studies involving a drug included patients with more mild to moderate forms of obesity (BMI < 35), suggesting that weight-based dosing with the use of actual body weight is applicable. When such studies with direct applicability to a particular patient are not available, the clinician will likely have to extrapolate from the evidence that does exist; often, this evidence is limited to pharmacokinetic investigations where an assessment of dose proportionality is needed. For the majority of drugs commonly used in the ICU setting, there is little evidence to suggest the use of actual body weight for weight-based dosing regimens in more severe forms of obesity[15]. The recommendation for the use of actual body weight for maintenance dosing of vancomycin is a notable exception, not the rule, for most of these drugs. This is not totally unexpected given that many of these drugs are eliminated by the kidneys and the most accurate estimations of creatinine clearance in more extreme forms of obesity have been made using equations based on lean or another form of adjusted body weight[16]. Similarly, loading doses of drugs that primarily distribute into the intravascular compartment would likely require dosing based on a lean or adjusted body weight for weight-based dosing regimens given that blood volume does not increase

Table 8 Conceptual framework for dosing medications in obese patients[1]

Step 1
Evaluate the clinical investigations involving the medication to determine the degree of obesity in the patients under study and the weight descriptor used for dosing, which is usually actual body weight (ABW) in studies leading to medication approval. Determine if the patient under consideration appears to fit the profile of the patients in the study; be particularly cautious if the patient is extremely obese. If the patient appears to fit the profile of the patients in the studies, use the weight descriptor. If not, proceed to Step 2
↓
Step 2
If the patient does not fit the profile of the patients in the clinical investigations, search the literature for pharmacokinetic studies involving the medication in obese patients. Assess whether the pharmacokinetic parameters of the medication appear to increase proportionately with increasing weight suggesting that use of ABW may be appropriate. If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 3
↓
Step 3
If the patient does not fit the profile of the patients in the clinical investigations and if no pharmacokinetic studies involving the specific medication in obese patients are available, evaluate the literature for dosing studies in obese patients with medications that have similar physicochemical and pharmacokinetic parameters (*e.g.*, medications in the same class). If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 4
↓
Step 4
If no relevant studies can be found, and particularly if the patient is extremely obese, assess whether an alternative medication (where more is known about dosing in obese patients) might be appropriate. If there is no equivalent or better medication option available, proceed to Step 5
↓
Step 5
Assess the benefits and risks of using ABW for dosing using step 5a for weight-based dosing or 5b for non-weight based dosing

Step 5a
If weight-based dosing (*e.g.*, mg/kg) is being used, assess whether the potential benefits of using ABW (*e.g.*, need to reach therapeutic range quickly) are likely to exceed the potential risks of over-dosing. If the patient under consideration is substantially heavier than the patients in the investigations or if no studies are available, assess whether a lean body weight or adjusted body weight equation might be preferable, especially in medications with a narrow therapeutic range and small (*e.g.*, < 0.2 L/kg) to moderate (*e.g.*, 0.2 to 1 L/kg) volumes of distribution that are cleared primarily by glomerular filtration
Step 5b
If non-weight-based dosing (*e.g.*, mg/dose) is being used, assess whether the potential benefits of using a larger dose are likely to exceed the potential risks of over-dosing if the patient under consideration is substantially heavier than the patients who were enrolled in the clinical investigations involving the medication, and if the medication has a narrow therapeutic range and a moderate (0.2 to 1 L/kg) to large (> 1 L/kg) volume of distribution

[1]Should always take into account potential co-morbidity confounders such as renal or liver dysfunction when determining dosing regimens. Reprinted with permission from Erstad[57].

proportionally to increasing fat weight; importantly, the standard variation of both creatinine clearance and plasma volume measurements become larger in more severely obese patients[17,18].

Recommendations
For patients with mild-moderate forms of obesity (BMI < 35), dosing recommendations provided in the product information and other reputable drug information sources are usually appropriate since the studies that led to drug approval likely included such patients. The issue of dosing is more complicated in patients with more extreme forms of obesity since such patients are often either excluded from studies or included in such small numbers that a sub-analysis of data is inadequately powered to provide meaningful conclusions. When dosing these patients in the ICU setting the clinician will likely need to extrapolate dosing information from other similar drugs (*e.g.,* drugs in the same structural class) when such information is available and from investigations evaluating the drug's physicochemical and pharmacokinetic properties. Finally, the benefit *vs* risk assessment of using actual body weight for weight-based dosing of a drug should take into account the fact that most renally-eliminated drugs studied to date have not exhibited dose proportionality in patients with extreme forms of obesity; in other words, renal clearance of the drug does not increase proportionately with increasing body weight suggesting that an adjusted weight would be more appropriate to use when designing weight-based dosing regimens in severely obese patients.

Drug dosing in patients who are underweight, short, or have amputations or missing limbs
Based primarily on indirect evidence, underweight or short (assuming relatively normal body weight for height) patients are usually dosed on the lower end of dosing ranges for non-weight based dosing regimens. Such dosing is predicated on the assumption that the proportion of lean or metabolically active tissue is similar to that of patients of more normal weight and stature. However, an interesting issue arises when it is decided to use ideal body weight for a drug that has weight-based recommendations. The formulas most commonly used for dosing ideal body weight are based

on calculations that assume the patient is at least 5 feet tall. For example, for a male, one ideal body weight equation is calculated by adding 2.3 kg for each inch above 5 feet tall with a 50 kg base weight for the first 5 feet. While not based on any solid evidence, some clinicians have estimated the ideal body weight for a person less than 5 feet tall by subtracting 2.3 kg for each inch below 5 feet. Others have used regression analysis, typically on older data, to derive estimations for individuals less than 5 feet. With any of these methods, the estimates are likely to be less precise the shorter the patient. Similar issues would arise when estimating ideal body weight in patients who are missing body parts such as an arm or leg.

Recommendations

For non-weight-based dosing, usual or slightly lower than usual doses likely will suffice, assuming all other factors such as body weight and renal function are near normal. For weight-based dosing, there are a couple of options. Particularly for drugs with a wide therapeutic index, one could use actual body weight with the assumption that the missing limb had metabolic activity similar to the rest of the body. Also as above, the issue arises as to which weight to use when calculating an ideal body weight. One method that has been used in this situation for nutritional assessment is based on body part proportionality[19]. With this method, different body segments are assigned a percentage of total body weight. For example, a leg with a foot might comprise 16% of the total body weight, so the ideal body weight calculation in a patient with a leg amputation would be lowered by 16%. For an obese patient with this same amputation, the ideal body weight would be calculated in the same manner. If this same obese patient was being dosed by some other adjusted body weight equation (e.g., ideal weight plus 40% of the excess weight), then the ideal body weight that takes into account the missing leg would be calculated first and used in the adjusted body weight equation. It is unknown if these methods of ideal body weight correction are more accurate or appropriate than an uncorrected (and easier to calculate) ideal body weight estimation for drug dosing.

None of these methods has been validated; further, the methods for calculating ideal body weight in patients of short stature do not take into account possible fat weight associated with obesity. If used, any of these dosing estimations should have some form of verification through therapeutic drug monitoring if available and/or through pharmacologic endpoints.

Drug choice or dosing in pregnancy

In general, pregnant or postpartum women account for a relatively small percent of ICU admissions, although the numbers are dependent on the type and location of hospital[20]. Traumatic injuries occur in approximately 7% of pregnancies in the United States[21]. Apart from the direct adverse consequences of the trauma or underlying disease states in the pregnant woman, there are special considerations for drug dosing not only because of physiological changes in the mother, but also because of potential fetal risk. The current FDA labeling of drugs is based on risk categories A, B, C, D, and X, although this system is currently undergoing revision by the FDA because of confusion associated with risk/benefit interpretation. It is important to note that these categories do not represent a linear increase in risk, since categories C, D, and X each involve a risk/benefit assessment. Such an assessment should take into account the timing of drug administration is important; for example, the critical period for embryonic organ formation is during weeks 3 to 8 post-conception. It has been estimated that approximately 66% of all drugs are category C[22]. In light of these categorical limitations, other references have been developed to provide the clinician with more information for drug use in pregnancy[23]. However, the quality and usefulness of the data in such sources is a function of the method of data collection, which in the case of fetal adverse drug events in pregnancy is data from case reports and registries. Both the numerator (i.e., number of subjects with a reported adverse event) and the denominator (total number of subjects receiving the drug) are unlikely to be accurate with these collection techniques, so a true incidence is unknown, assuming causality does exist. Also largely unknown is how the duration of drug exposure relates to potential fetal harm.

The assessment of drug risk vs benefit in critically ill pregnant women is particularly complicated since potential delays in therapy could lead to adverse outcomes for the mother and fetus. Often initial life-saving interventions are performed without knowing whether or not a critically ill woman is pregnant. There is a saying that as maternal health goes, so goes fetal health[24]. Recommendations by the American College of Obstetricians and Gynecologists specifically state that necessary medications should not be withheld to due to fetal concerns[25]. Usually, there are at least a few potential alternatives in which case the decision is made based on factors such as drug risk category, other drug toxicities and experience with the drug in pregnancy. The two examples of severe sepsis/septic shock and hypertensive crisis will be used to illustrate some of these considerations. In general, the recommendations for fluids, vasoactive agents, and antimicrobial agents in pregnant women with severe sepsis or septic shock are the same as for non-pregnant women[26,27]. In fact, the recommendations in the Surviving Sepsis Guidelines have been endorsed by respected organizations such as the Royal College of Obstetricians and Gynaecologists[28]. Prior to widespread endorsement of these guidelines, arguments for the use of specific agents such as choice of vasopressors was often made on the basis of animal models that focused on issues such as uterine blood

flow[29]. Current thinking is that the potential mortality benefits of optimal resuscitation with a more potent agent such as norepinephrine outweigh more local or regional blood flow concerns[26]. In cases where there is no clear drug of choice, as might occur with antimicrobial selection, drugs with well-described toxicities (*e.g.,* aminoglycoside nephrotoxicity) should only prescribed when similarly efficacious, but less toxic agents are not an option (as should be the case in non-pregnant women).

In contrast to severe sepsis and septic shock that have one widely accepted guideline with treatment recommendations aimed at reducing mortality, there are multiple guidelines and recommended agents for treating hypertensive crisis during pregnancy. There is no high level evidence to suggest any differences in antihypertensive agents using mortality as the outcome of interest, so the choice-of-drug decision is heavily based on toxicity considerations. In the past, IV hydralazine was routinely recommended as a first-line choice for hypertensive crises including preeclampsia, but it is increasingly be considered a second-tier agent[30,31]. Currently, IV labetalol is considered as a preferred first-line agent for hypertensive crisis in pregnant women in the majority of treatment guidelines[32], but alternatives exist for refractory cases as long as one considers potential toxicities especially with more prolonged use (*e.g.,* methemoglobinemia due to nitroglycerin)[33,34]. An example of a class of antihypertensive agents that should almost always be avoided during pregnancy is the angiotensin-converting enzyme inhibitors such as intravenous enalaprilat that have a boxed warning about potential fetal injury and death when given during the second and third trimesters of pregnancy.

There are far more questions than answers when it comes to supportive care drug (*e.g.,* analgesics, sedatives) use in the critically ill pregnant patient, and the risk/benefit assessment must include potential harm to the fetus. The difficulty in such assessments is illustrated by the choice of a sedative agent for a pregnant critically ill patient. In the not too distant past, benzodiazepines were the drugs of choice for ICU sedation. However, benzodiazepines cross the placenta and are labeled as pregnancy category D. Additionally, alternative sedative agents are now available including propofol (category B) and dexmedetomidine (category C), but there is little data on longer-term use in pregnant women. This can lead to difficult decisions in pregnant women with prolonged ICU stays[35]. Table 9 lists some of the more common drugs used in the ICU setting and their implications for use in pregnant women. This table is meant to supplement other materials including more specific recommendations in FDA-approved product information brochures (*e.g.,* the use of preservative-free heparin and low molecular weight heparin preparations).

Recommendations
The drug management principles for critically ill pregnant patients are the same as for non-pregnant patients in the sense that potentially life-saving medications should not be withheld when no similarly efficacious therapies exist. When the situation is less dire and when more than one drug option is available, the benefit *vs* risk assessment should take into account the limited information on potential maternal/fetal harm that is available. Some decisions will be more clear-cut than others. For example, there are multiple agents available for treating hypertensive episodes in the ICU, so there would rarely if ever be a need to use sustained dosing with an agent like an ACE-inhibitor that has documented potential for fetal harm. For more difficult therapeutic dilemmas, additional expertise such as that by genetic counseling experts may be helpful.

Drug choice or dosing in extracorporeal membrane oxygenation
Long-term ECMO was first used in an adult patient with respiratory failure in 1972, but initial enthusiasm was dampened when a randomized trial of ECMO for adult respiratory distress syndrome (ARDS) was stopped due to futility[36]. Enthusiasm for this technique has been renewed based on reductions in mortality noted in more recent randomized and cohort studies of patients with severe ARDS, and in particular, H1N1-related ARDS[37,38]. From a medication standpoint, much of the emphasis has been on anticoagulation strategies and monitoring, which is not surprising given that bleeding and thrombosis are important causes of ECMO-associated morbidity and mortality[39]. However, ECMO may also alter the pharmacokinetic, pharmacodynamics and therapeutic properties of medications that must be administered to patients receiving this modality - that is the focus of this discussion. One recent review of pharmacokinetic changes associated with ECMO concluded that "published literature is insufficient to make any meaningful recommendations for adjusting therapy for drug dosing"[40]. Fortunately, there are ongoing systematic studies that are investigating the actions of a variety of drugs commonly administered during ECMO procedures[41,42]. The studies involving drug administration in conjunction with ECMO fall into 3 general categories: *in vitro* studies related to physicochemical properties of drugs (*e.g.,* drug binding to ECMO circuitry); pharmacokinetic studies; and clinical trials. The *in vitro* studies are demonstrated by a recent investigation that evaluated potential drug sequestration in ECMO circuitry by 5 drugs commonly administered to critically ill patients. Equivalent doses of 2 opioids (fentanyl, morphine), 1 sedative (midazolam), and 2 antimicrobials (meropenem, vancomycin) were studied in ECMO circuits and polyvinylchloride jars with fresh human whole blood[43]. There were no substantial issues of stability or sequestration with vancomycin or morphine, but meropenem recovery was low (20% *vs* 42% in ECMO *vs* control, respectively) suggesting temperature-related stability issues, and fentanyl and midazolam recovery were significantly lower in the

Table 9 Implications of medications for the pregnant critically ill patient

Indication/class	Specific drug	FDA[3]	Comments[1]	Indication/class	Specific drug	FDA[3]	Comments[1]
Sedative	Propofol	B		Anticoagulant	Enoxaparin	B	
	Midazolam	D			Heparin	C	
	Lorazepam	D	Risk (1st and 3rd trimesters)		Fondaparinux	B	
	Dexmedetomidine	C			Argatroban	B	
Analgesic	Morphine	C	Risk (3rd trimester)	Corticosteroid	Methylprednisolone	C	
	Fentanyl	C	Risk (3rd trimester)		Hydrocortisone	C	Data suggest risk
	Hydromorphone	C	Risk (3rd trimester)	Antifungal/ antiviral	Voriconazole	D	
Delirium	Quetiapine	C	Risk (1st and 3rd trimesters)		Fluconazole	D	Data suggest risk if > 400 mg/d
	Haloperidol	C			Micafungin	C	
Pulmonary hypertension	Epoprostenol	B			Amphotericin	B	
	Treprostinil	B			Acyclovir	B	
	Iloprost	C		Antibiotic	Azithromycin	B	
Bronchodilator	Tiotropium	C			Aztreonam	B	
	Ipratropium	B			Cefazolin	B	
	Albuterol	B			Cefepime	B	
	Levalbuterol	C			Cefoxitin	B	
Vasoactive	Epinephrine	C	Data suggest risk		Ceftriaxone	B	
	Norepinephrine	C	Data suggest risk		Ciprofloxacin	C	Data suggest low risk
	Vasopressin	C			Clindamycin	B	
	Phenylephrine	C	Data suggest risk		Linezolid	C	
	Dopamine	C			Meropenem	B	
	Dobutamine	B			Metronidazole	B	Data suggest low risk
	Milrinone	C			Moxifloxacin	C	Data suggest low risk
Antiarrhythmic	Diltiazem	C	Data suggest low risk		Piperacillin/ tazobactam	B	
	Amiodarone	D	Data suggest risk		Vancomycin	C	
	Digoxin	C		Anti-seizure[2]	Levetiracetam	C	
Antihypertensive	Labetalol	C	Data suggest low risk		Phenytoin	D	
	Esmolol	C		Paralytic	Rocuronium	C	
	Hydralazine	C	Risk (3rd trimester)		Cisatracurium	B	
	Magnesium sulfate	D			Vecuronium	C	
	Nitroglycerin	C	Data suggest low risk		Succinylcholine	C	
	Sodium nitroprusside	C	Data suggest risk				
	ACE-inhibitors	D	Data suggest risk (2nd and 3rd trimesters)				
Diuretic	Furosemide	C	Data suggest low risk				
	Mannitol	C					
GI/antiemetic	Pantoprazole	B	Data suggest low risk				
	Famotidine	B					
	Ondansetron	B					
	Metoclopramide	B					
	Erythromycin (non-estolate)	B					

[1]Human data to suggest risk based on data from Briggs et al[23]; [2]Pregnant women exposed to AEDs should register with the North American Antiepileptic Drug Pregnancy Registry (888-233-2334); [3]Refers to FDA pregnancy rating category. FDA: Food and Drug Administration; ACE: Angiotensin converting enzyme.

ECMO groups (3% vs 82%, P = 0.0005 and 13% vs 100%, P = 0.01, respectively) suggesting lipophilic-drug sequestration. Dosing modifications based on these ex-vivo findings of meropenem instability requires further study, but there are potential implications for other thermo-labile medications. In contrast to these findings that suggest no stability or sequestration concerns with morphine, another in vitro study found that 40% of a single dose of morphine was removed by ECMO tubing or circuitry[44]. The differences in morphine disposition in these 2 studies may be a function of differing methodologies, but they illustrate the problem with excessive reliance on in vitro data.

Pharmacokinetic studies have the potential advantage of measuring blood drug concentrations in vivo but these studies require the availability of a drug assay, presume a relationship between a surrogate marker (i.e., the blood concentration of the drug or its active metabolite) and therapeutic effect, and are difficult to perform in critically ill patients. Pharmacokinetic studies are commonly employed for investigations of antimicrobial agents used to treat infections associated with ECMO. For example, antiviral medications have been used in combination with ECMO for treating severe influenza infections. Pharmacokinetic studies involving the neuraminidase inhibitor oseltamivir given enterally in critically ill adult patients on ECMO suggest that normal doses of oseltamivir (i.e., 75 mg twice daily) are appropriate

Table 10 Drug dosing considerations in adult patients receiving extracorporeal membrane oxygenation

Drug dosing recommendations for an adult on ECMO are unlikely to be evidenced-based
Data from neonatal case reports, case series or studies may not apply to adults
Data from one drug may not be applicable to another even from the same class
Drug regimen recommendations in critical care guidelines may not apply to patients on ECMO
Organ dysfunction apart from the lung and heart complicate interpretation of literature
The contribution of distinct physicochemical properties of drugs to sequestration is unclear
Hydrophilicity or lipophilicity appear to be important factors affecting pharmacokinetics
The therapeutic actions of drugs are not consistently predictable by pharmacokinetics
The design and properties of the equipment change over time with implications for dosing
The priming solution such as blood or blood-derived products may affect dosing

ECMO: Extracorporeal membrane oxygenation.

unless a patient has concomitant renal dysfunction in which case dose reduction may be in order[45-47]. Case report pharmacokinetic data in patients undergoing ECMO is available for other antimicrobials including the antifungal agents caspofungin and voriconazole[48]. Similar to pharmacokinetic studies, there are a few studies using laboratory parameters as surrogate markers of clinical effect. For example, in critically ill patients on ECMO who were receiving argatroban for suspected heparin-induced thrombocytopenia, argatroban requirements based on activated partial thromboplastin time monitoring were found 10-fold lower than the 2 μg/kg per minute dose recommended in product labeling[49].

There are limited clinical studies involving drug choice or dosing in patients undergoing ECMO and the data from these studies does not always seem to corroborate data from the *in vitro* and pharmacokinetic investigations. For example, one retrospective study found that morphine and midazolam requirements increased, but fentanyl requirements remained unchanged with continued dosing over time in adult patients on ECMO for cardiorespiratory failure[50]. On the other hand, neonates on ECMO required less supplemental analgesia when given morphine infusions *vs* fentanyl infusions in a historical control group[51]. The patients in the morphine group all experienced less withdrawal and were discharged earlier (P = 0.01 for both). Table 10 lists some of the more important considerations when evaluating published literature and devising dosing regimens in critically ill patients receiving ECMO.

Recommendations
The paucity of literature regarding drug dosing in ECMO with relevant clinical outcomes precludes any meaningful evidence-based recommendations. Therefore, the clinician must extrapolate information from the limited *ex vivo* and pharmacokinetic studies that have been conducted for selected drugs taking into account changes in ECMO technologies in recent years that may influence previous study findings. *Ex vivo* studies suggest that lipophilic drugs are particularly prone sequestration by ECMO circuitry. For drugs titrated to clinical effect such as opioids, the clinician may either choose to use less lipophilic agents such as morphine (assuming no renal failure) or use more lipophilic agents like fentanyl with the appreciation that higher than expected doses may

be needed. For some drugs, therapeutic drug monitoring may be available and useful. For lipophilic or thermo-labile (*e.g.,* carbapenems and ampicillin) drugs that are not titrated to clinical effect and for which therapeutic drug monitoring is usually not available, the clinician must be alert for potential therapeutic unresponsiveness or failure due to inadequate dosing. Table 11 lists the pharmacokinetic and physicochemical characteristics of drugs commonly used in critically ill patients in order to help with drug selection and dosing when data from clinical trials involving ECMO are not available.

Drug choice or dosing during plasma exchange
Plasma exchange (aka plasmapheresis) is another modality that has drug-dosing related concerns. If one assumes a normal plasma volume of approximately 4 L for an 80 kg patient, then plasma exchange at a rate of approximately 50 mL/kg over 2 h would remove 2 plasma volumes and more than 80% of all solutes[52]. Much of the experience with plasma exchange has been case report data associated with overdosing or poisonings. The AABB and the American Society for Apheresis has concluded that there is little or conflicting evidence for the latter indications and that such use represents "heroic" of "last-ditch" efforts[53]. Apart from the intended use of plasma exchange for toxicological problems, there is the unintended effect of plasma exchange on drugs being used in usual therapeutic doses.

Drugs most likely to be eliminated by plasma exchange are those with small volumes of distribution that approximate extracellular fluid stores (less than 0.2 L/kg) and those with plasma protein binding of at least 80%[54]. Since plasma proteins and bound drugs are removed in tandem with fluid in plasma exchange, there is increased drug removal with increased protein binding in contrast to hemodialysis that preferentially removes unbound drugs. The timing of drug administration relative to onset of plasma exchange is critical to the amount of drug elimination. Hydrophilic drugs with small volumes of distribution and high protein binding would be particularly susceptible to removal if initiated after plasma exchange has begun. Lipophilic drugs with larger volumes of distribution would not be expected to have substantial removal by plasma exchange, presuming

Table 11 Pharmacokinetic and physicochemical properties of drugs commonly used in the intensive care units[1]

Indication/class	Specific drug	LogP	Pb (%)	Vd (L/kg)
Sedative				
	Propofol	4.16	98	60
	Midazolam	3.33	97	2
	Lorazepam	3.53	91	1.3
	Dexmedetomidine	3.39	94	1.3
Analgesic				
	Morphine	0.9	35	3
	Fentanyl	3.82	83	5
	Hydromorphone	1.62	20	1.2
Delirium				
	Quetiapine	2.81	83	10
	Haloperidol	3.66	92	18
Antiarrhythmic				
	Diltiazem	2.37	80	5
	Amiodarone	7.64	98	70
	Digoxin	2.37	25	6
Antihypertensive				
	Labetalol	1.89	50	5
	Esmolol	1.82	55	3
	Hydralazine	0.75	87	4
GI/antiemetic				
	Pantoprazole	2.18	98	0.15
	Famotidine	-2	18	1.2
	Ondansetron	2.35	73	2
	Metoclopramide	1.4	30	4.4
	Erythromycin	2.6	85	0.6
Anticoagulant				
	Enoxaparin	-8.3	80	0.07
	Heparin	NA	NA	0.05
	Fondaparinux	-10	94	0.1
	Argatroban	-0.97	54	0.17
Corticosteroid				
	Methylprednisolone	1.56	78	1.1
	Hydrocortisone	1.28	95	0.5
Antifungal/ antiviral				
	Voriconazole	1.82	58	3
	Fluconazole	0.56	11	0.8
	Micafungin	-6.3	99	0.39
	Amphotericin	-2.3	95	1.8
	Acyclovir	-1	9-33	0.6
Antibiotic				
	Azithromycin	2.44	51	0.44
	Aztreonam	-3.1	56	0.17
	Cefazolin	-1.5	80	0.14
	Cefepime	-4.3	20	0.23
	Cefoxitin	0.29	75	0.26
	Ceftriaxone	-1.8	95	0.14
	Ciprofloxacin	-0.81	35	2.5
	Clindamycin	1.04	93	2.5
	Linezolid	0.64	31	0.64
	Meropenem	-4.4	2	0.36
	Metronidazole	-0.46	25	1
	Moxifloxacin	-0.5	50	2
	Piperacillin/ tazobactam	-0.26		0.1
	Vancomycin	-3.1	55	0.7
Anti-seizure				
	Levetiracetam	-0.59	8	0.6
	Phenytoin	2.15	90	0.7

[1]LogP is the octanol-water partition coefficient and is expressed as the ratio of the solubility of a compound in octanol (non-polar solvent) to its solubility in water (polar solvent). Some of the data from this table (particularly the log P values) were obtained from www.drugbank.ca. NA: Not applicable.

the plasma exchange is not initiated until after the initial distribution phase of the drug has taken place. There is case report data for some drugs that confirm these generalizations. For example, voriconazole that has a volume of distribution slightly over 4 L/kg and protein binding of approximately 58% would not be expected to have significant removal by plasma exchange and this was confirmed in a pharmacokinetic study involving a patient receiving plasma exchange in conjunction with voriconazole for an invasive aspergillosis infection[55].

Recommendations
Once it is known that a patient will undergo plasma exchange, the clinician must evaluate each of the drugs being administered to the patient and attempt to devise an optimal dosing regimen or find alternative drugs unlikely to be affected by the procedure (*i.e.,* large volume of distribution and low protein binding). The evaluation must take into account the specific plasma expander being used as a replacement fluid, since albumin or albumin-containing fluids like fresh frozen plasma influence drug binding. Additionally, the evaluation should consider the pharmacokinetics of the drug, the timing of the drug relative to the plasma exchange procedure, co-morbidities such as renal failure that might alter normal kinetics, and the limited published literature that is available. Table 11 lists pharmacokinetic and physicochemical properties of drugs commonly used in critically ill patients that can be used to help predict drug disposition in association with plasma exchange.

CONCLUSION
Special populations of ICU patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

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