Review Article

Anti-infective Dosing for Obese Adult Patients: A Focus on Newer Drugs to Treat Methicillin-resistant *Staphylococcus aureus* Acute Bacterial Skin and Skin Structure Infections

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ABSTRACT

Purpose: Obesity is recognized to be a risk factor for acute bacterial skin and skin structure infections (ABSSSIs) that are associated with methicillin-resistant *Staphylococcus aureus* (MRSA). Several new antimicrobial agents have been introduced to treat MRSA-related ABSSSI and are dosed with and without regard to weight. This review seeks to explain the pharmacokinetic and pharmacodynamic (PK-PD) rationale for initial and maintenance dosage selection of these newer agents in obese adults.

Methods: A PubMed search was performed using the key words obese or obesity, pharmacokinetics, and the name of each MRSA active drug evaluated in this review. Major themes were identified through a review of this literature. A synopsis of key findings from population PK studies (including reference sources) and independent studies of the PK properties of each new MRSA active agent used to treat ABSSIs were reviewed to derive practical dosing considerations.

Findings: Clinical trials of ABSSSIs have increasingly incorporated individuals across a wide body size spectrum. This inclusion of obese adults has been reflected in population PK analyses that have permitted the evaluation of weight and other body size descriptors. In general, the volume of distribution is higher in obese patients, suggesting the need for higher initial (loading) doses if PK bioequivalence is desired. Less certainty exists with selection of a higher maintenance dose, especially for antimicrobial agents with time-dependent PK-PD properties. Selection of higher maintenance doses through alternate scaling approaches in obese patients can be justified on an individual clinical basis.

Implications: Maintenance dose modification of several MRSA-targeted anti-infective agents is unlikely to be necessary in obese patients and should be capped if dosed on total weight or this higher dose justified with therapeutic drug monitoring. (*Clin Ther.* 2016;38:2032–2044)

Key words: dosing, drug, MRSA, obesity, pharmacodynamics, pharmacokinetics.

INTRODUCTION

Obesity is no longer a "First World" problem with more than half a billion obese adults globally who now outnumber those who are underweight.[1,2] The American Council on Exercise classifies women and men as obese when their proportion of body fat exceeds 32% and 25%, respectively.[3] Easier access to energy-dense and sugar-laden foods coupled with more sedentary lifestyles continues to shift our body compositions toward increased adiposity. In the United States, the average adult today is approximately 25 pounds heavier than his or her grandparents were on average 60 years ago.[4,5] Although

Accepted for publication July 22, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.07.094
0149-2918/$ - see front matter

our definition of obesity has changed over this time period, these trends for increased adiposity are unmistakable.[6]

Historical definitions of obesity in the United States began with the use of weight-for-height tables generated by the Metropolitan Life Insurance Company in the 1940s and 1950s. These tables were used to define "ideal weight" and "desirable weight" for men and women based on height and frame size.[6] Reliance on both height and weight has been central to the quantitative definition of obesity because use of weight alone is less informative of body composition. However, misclassification errors occur with these simple metrics because more athletic individuals have a higher muscle-to-fat ratio. The common definition of obesity today stems from the Quetelet index or body mass index (BMI) that is the weight in kilograms divided by height in square meters with a value ≥ 30 kg/m^2.[6] This definition was adapted by the World Health Organization in 1997 and subsequently adapted by the National Heart, Lung, and Blood Institute expert panel in 1998. This time line is important because our definitions of obesity changed during the era of antimicrobial discovery, knowledge of pharmacokinetic-pharmacodynamic (PK-PD) properties, emergence of pharmacometrics as a discipline, and the regulatory framework to justify antimicrobial dosage selection in clinical trials.[7,8] A plethora of antimicrobial agents targeting methicillin-resistant *Staphylococcus aureus* (MRSA) have been introduced into the marketplace over the past two decades.[9] This pathogen is a common cause of acute bacterial skin and skin structure infections (ABSSSIs), and obesity is a recognized risk factor for this infection.[10–13] Anti-infective agents used to treat ABSSSIs associated with this pathogen span multiple pharmacologic classes, have distinct PK-PD properties, and are dosed by weight and non–weight-based paradigms. As a consequence, this review seeks to inform the reader on empiric and alternate approaches to antimicrobial dosage selection in obese adults using vancomycin and newer agents to treat MRSA-associated ABSSSIs as exemplars.

PK-PD CONSIDERATIONS

The activity of antimicrobial agents can be optimized by selecting dosage regimens that create concentration–time profiles that maximize the rate of bacterial inhibition or killing. Over the past 60 years, we have broadly categorized this PK-PD optimization to be concentration dependent or time dependent.[14] Concentration-dependent antimicrobial agents are optimized by ensuring that the C_{max} and the closely correlated parameter of AUC achieve a certain target value. A classic example of concentration-dependent optimization includes the use of high-dose extended interval aminoglycoside dosing for Gram-negative–related infections. In contrast, time-dependent antimicrobial agents are optimized by ensuring that the concentration profile remains above a concentration threshold for a specified proportion of the dosing interval.[14,15] The β-lactams are a key antimicrobial class in which continuous infusion and extended interval infusion regimens are used to maximize the time above a threshold concentration. The MIC serves as the most common antimicrobial potency threshold value. The activity of concentration-dependent antimicrobial agents is predicted by the C_{max}-to-MIC (C_{max}:MIC) and AUC-to-MIC (AUC:MIC) ratios. Although the activity of time-dependent antimicrobial agents are better predicted by time above the MIC ($T_{>MIC}$) but also correlate with the AUC:MIC ratio because AUC is a mathematical function of both concentration and time.

Figure 1 illustrates the simulated concentration–time profile of an antimicrobial agent administered by variable rates of infusion. This figure serves to illustrate several points about concentration–time profiles relative to an MIC value of 32 mg/L, for example. The first point that can be made is that slower rates of infusion may not achieve the concentration target unless an initial loading dose is administered. This is akin to the effects of obesity on the V_d.[16] Larger adults typically have a larger V_d that is noted by a lower systemic (plasma) C_{max} concentration and may need a loading dose to achieve this. However, maintenance of this larger dose in obese patients may be unnecessary by the third dose for a time-dependent antimicrobial agent because all the illustrated regimens achieve similar $T_{>MIC}$ values. This point of an initial higher but standard maintenance regimen in obese patients is most applicable to agents such as linezolid.[16]

Although not easy to visualize, the second point in this illustration is that all regimens achieve the same AUC over this period of time because the dose is identical in this simulation. The AUC is affected by the dose and clearance (CL) of the agent from systemic circulation.

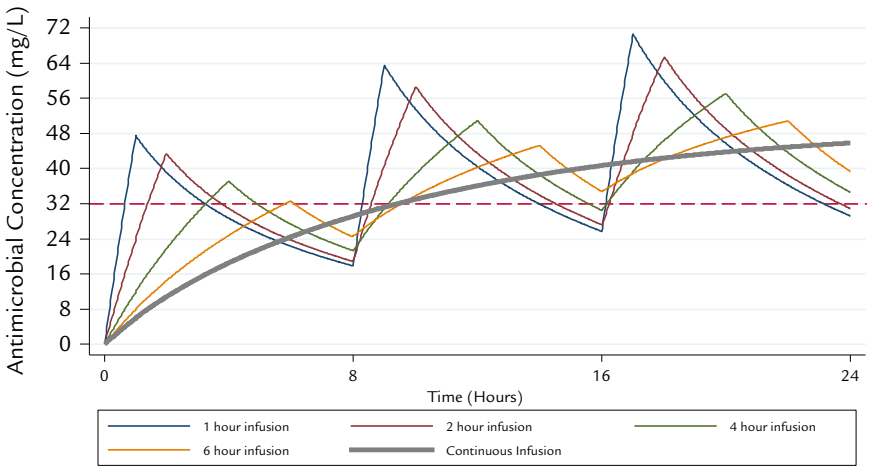

Figure 1. Simulated antimicrobial concentration–time profile by administering the same dose every 8 hours with variable rates of infusion over this 24-hour dosing period and a reference value of 32 mg/L.

Obese patients can have and enhanced CL, but often this parameter is no more than 50% above that in a normal-weight individual.[16–18] So higher maintenance doses may be necessary, but most often these are not proportionate to weight. The third point is that the C_{max} values will always be lower for longer rate infusions, which is comparable with oral drug administration such as the profile of oral linezolid compared with intravenous linezolid.[19] If an agent has a concentration-dependent PK-PD profile predicted by C_{max}, then shorter rate infusion doses will best optimize that profile. Daptomycin for example can be administered rapidly as a 2-minute infusion to best optimize that profile. Figure 2 illustrates the concentration–time profile expected with daptomycin administered at a dose of 500 mg (4 mg/kg in a 125-kg individual) by the standard 30-minute versus a 2-minute infusion using the population PK model.[20] As reported, a dose of 640 mg (5.1 mg/kg) would achieve a similar C_{max} in this individual as the lower dose administered as a 2-minute infusion but will have a higher AUC (as expected) and time above a threshold value. In this illustration, that threshold value is 24.3 mg/L, a concentration suggested to be predictive of creatine phosphokinase elevations.[21] On a theoretical level, if the bactericidal effects of daptomycin are predicted by the C_{max}, then use of short infusions could negate the need for higher doses at standard infusion rates. Thus, the rationale to raise the dose, change the interval, or modify the rate of infusion depends on the PK-PD properties of the antimicrobial in question.

INITIAL ANTIMICROBIAL DOSE SELECTION AND OBESITY

Obese patients may require a larger initial dose than average-sized patients, but the dose calculation is often not proportionate to their total weight.[22] In practical terms, if the therapeutic index is wide, then use of total body weight (TBW)-based dosing for the first dose often carries an acceptable risk-to-benefit (risk:benefit) ratio especially if the obese patient is critically ill.[23] So the empiric approach to initial dose selection may occur through consideration of body size. Clearly, the acceptability of TBW-based dosing diminishes as the individual increases in size. Alternate body size descriptions such as body surface area (BSA), ideal body weight (IBW), adjusted body weight (AdjBW), and lean body weight (LBW) have been applied as scalars to limit overdosage.[24–28]

A common approach in the pharmacology literature has been the use of TBW when this value is below IBW, IBW when TBW is no more than 1.2-fold higher than ideal weight, and AdjBW when TBW is >1.2-fold higher than ideal weight.[29] Figure 3 illustrates this expected weight that would be selected for dosing using this piecewise dosing approach based on height and weight data (n = 10,351) from the 2014 Behavioral Risk Factor Surveillance System.[30] This illustration highlights two major points; the first is that most US adults are currently expected to be within a 3-fold weight range, approximately 50 to 150 kg. The second

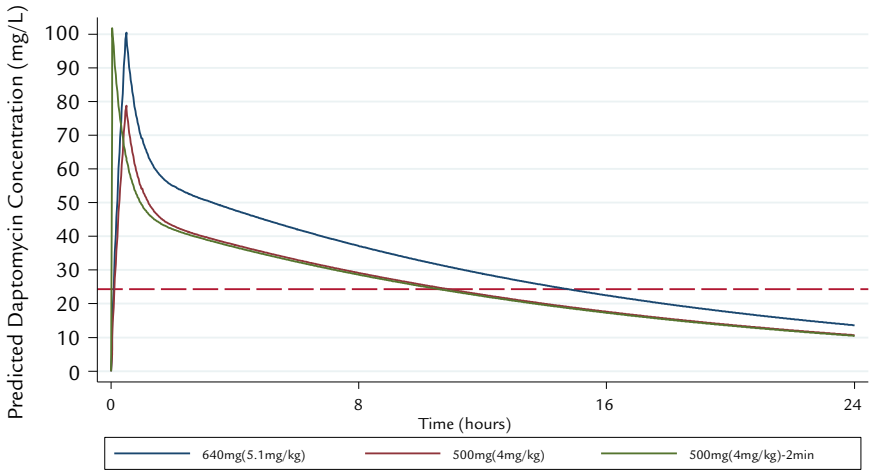

Figure 2. Comparison of the simulated daptomycin plasma concentration–time profile with administration of the same dose at 2 different rates of infusion relative to a higher dose at the standard rate of infusion

is that use of this piecewise approach of TBW, IBW, and AdjBW generates an approximately 2-fold range in weight values across the expected adult weight range. This 2-fold scaling approach is comparable with that of a BSA-based dosing method, which has been detailed previously.[22] However, there is considerable overlap between these alternate weight parameters when TBW is approximately <100kg. Similar (but a more continuous) dose scaling also occurs if the dose were calculated as obese patient dose = average dose × (obese patient weight/average weight)$^{\beta}$.[16] This mean β exponent value is often between 0.5 to 1.0 and is often fixed to 0.75 in population PK models that scale CL to weight.[22,31] In Figure 3, the relation of TBW to

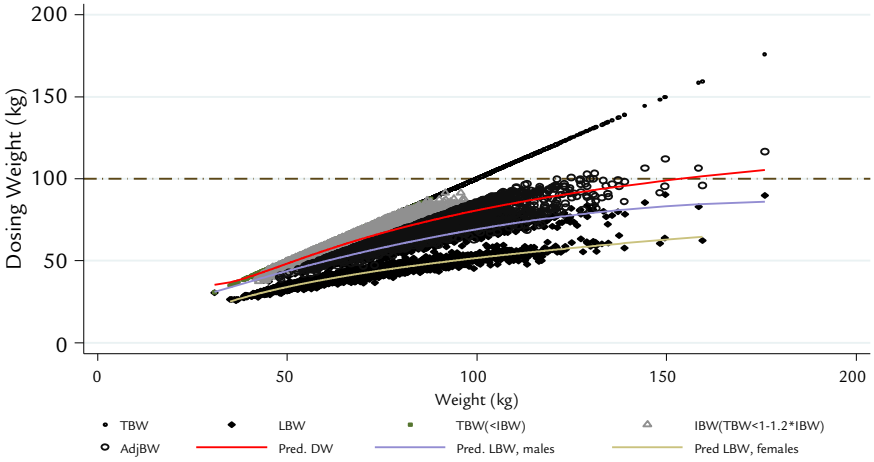

Figure 3. Expected dosing weight (DW) across the weight spectrum when using total body weight (TBW), lean body weight (LBW), ideal body weight (IBW), adjusted body weight (AdjBW), predicted (Pred.) DW as a piecewise function, and the Pred. values using LBW by sex. Use of the common piecewise approach of IBW, TBW, and AdjBW limit the calculation of DW values >120 kg. Use of LBW as the DW will systematically lead to calculation of lower doses in women and limits this value to <100 kg across the weight distribution.

piecewise alternate weights yields a mean β-exponent value of 0.713 (95% CI, 0.707–0.720) when modeled as a power function. In contrast, this β-exponent value is often fixed to 1.0 in population PK models that scale V_d to weight.[31] Finally, use of LBW as a dosing scalar will yield sex-specific distribution but will lead to computation of values lower than the piecewise approach stated earlier (Figure 3).[26] As should be obvious, use of a 10-mg/kg dose of a drug on LBW will lead to computation of lower doses than the piecewise dosing weight or TBW metrics and will require a higher value (>10 in this example) to compute isometric doses. Again from a practical perspective, if the desire is to achieve therapeutic concentrations with the first dose of an antimicrobial agent, then the initial (first) dose should be higher in an obese patient relative to a normal-weight individual. Continuing this higher initial dose as part of a maintenance regimen is less certain and requires drug-specific considerations.

MAINTENANCE ANTIMICROBIAL DOSAGE REGIMEN SELECTION AND OBESITY

The optimal maintenance dosage regimen of an antimicrobial in an obese adult primarily depends on individual drug CL and the PK-PD profile of the agent (Table I). Several clinical variables such as age, sex, height, weight, kidney function, liver function, drug–drug

Table I. Summary of the typical dosing regimens for major antimicrobial agents used to treat methicillin-resistant *Staphylococcus aureus*.

Drug	Pharmacodynamic Predictor of Effect	Typical Adult Dosage	Dosing Considerations in Obesity
Vancomycin	AUC:MIC, $T_{>MIC}$	15 mg/kg IV every 12 hoursl	Fixed-dosing strategy and TDM often used. Maintenance dose capped at 2 g per individual dose (>133 kg)
Daptomycin	AUC:MIC, C_{max}:MIC	4 mg/kg IV every 24 hours	Fixed-dosing strategy may be applicable, unclear rationale to use >500 mg/d (>125 kg)
Ceftaroline	$T_{>MIC}$	600 mg IV every 12 hours	Dosage adjustment in obesity is unlikely
Telavancin	AUC:MIC, C_{max}:MIC	10 mg/kg IV every 24 hours	Fixed-dosing strategy may be applicable, unclear rationale to use >1000 mg/d (>100 kg)
Oritavancin	AUC:MIC	1200 mg IV once as a 3-hour infusion	Limited clinical experience, but dose adjustment in obesity is unlikely
Dalbavancin	AUC:MIC	1000 mg IV followed 1 week later by 500 mg IV	Two-dose therapy; limited clinical experience, but dose adjustment in obesity is unlikely
Tigecycline	AUC:MIC	100 mg IV, then 50 mg IV every 12 hours	Use of higher doses can be associated with an increased risk of nausea and vomiting
Linezolid	AUC:MIC, $T_{>MIC}$	600 mg IV/PO every 12 hours	Highly variable pharmacokinetic profile, initial daily doses could be 50% higher in morbidly obese patients
Tedizolid	AUC:MIC	200 mg IV/PO every 24 hours	Short-course therapy (6 days); limited clinical experience, but dose adjustment in obesity is unlikely

AUC:MIC = AUC-to-MIC ratio; C_{max}:MIC = C_{max}-to-MIC ratio; TDM = therapeutic drug monitoring; $T_{>MIC}$ = time above the MIC.

interactions, drug–food interactions, and pharmacogenomic polymorphisms can influence PK system parameters.[8] Within this covariate milieu, obesity is often factored into the population PK model using TBW or BSA. Current estimates of kidney function also incorporate age, sex, and weight, and so this estimate serves as a composite parameter that can predict the CL of antimicrobial agents, including those that are not eliminated by the kidneys.[16] Obesity is associated with hepatic steatosis and can influence the cytochrome P450 2E1 isoenzymes system. However, this isoenzyme system does not play a significant role in antimicrobial drug metabolism.[17,18] Importantly, a reliable method to translate liver function into individual drug CL does not presently exist to aid maintenance dose selection.

In contrast, kidney function is quantified using biomarkers and clinical variable to provide an estimate of the glomerular filtration rate (eGFR).[32] Drug clearance mechanisms also depend on renal tubular secretion and reabsorption.[33] Various renal tubular transporters of the solute-like carrier and adenosine triphosphatase binding cassette families have been identified, but their role and functional changes in the setting of obesity are not well known.[34,35] Serum creatinine is the most common endogenous biomarker used to quantify kidney function (creatinine clearance) and undergoes glomerular filtration and proximal tubular secretion. The estimated creatinine clearance (eCLcr) is used to define drug dosing and relies most often on the Cockcroft-Gault equation that is a function of serum creatinine, age, TBW, and sex.[36] Any eCLcr or eGFR equation that relies on a single point estimate requires a fundamental expectation of homeostasis that is often not the case in acutely ill patients. Despite this limitation, both eGFR and eCLcr do serve as reasonable benchmarks to categorize patients as having normal or below normal kidney function. Unfortunately, dosing guidance based on eCLcr have most often been defined to lower the dose and not manage the alternate scenario of dose increment when kidney function is augmented.[37]

Obese subjects reported a 94% higher Bowman's pace volume and a 33% higher cross-sectional area of the proximal tubular epithelium relative to nonobese subjects.[38] These changes in renal histology correlate with observed glomerular hyperfiltration in younger extremely obese population.[39] This increase in normal kidney function can contribute to development of chronic kidney disease over time. Hence, estimation of kidney function is complicated in obese patients due to potential time and comorbidity (hypertension, diabetes) dependent changes in renal physiology.[32] This creates the potential for dosing misclassification illustrated by two potential clinical scenarios. A high eCLcr such as 180 mL/min would be estimated in a 50-year-old man who weighs 130 kg and has a serum creatinine of 0.90 mg/dL. Use of an alternate body size descriptor in the eCLcr equation such as AdjBW (100 kg) would perhaps lower this estimate to 138 mL/min. However, this value may be 2-fold higher than that of the "average patient" in the population and suggest the need for higher doses than the average. So, use of a standard dose could in theory lead to lower AUCs if the CL of this drug has a positive correlation with eCLcr.

The alternate scenario is also plausible when the serum creatinine is elevated. If the above scenario was changed such that the serum creatinine was 3-fold higher (2.7 mg/dL), the eCLcr would be computed as 60 mL/min (TBW) and 46 mL/min (AdjBW). The dosing of several antimicrobial agents such as ceftaroline are modified when the eCLcr is <50 mL/min. So, should the daily dose be reduced or follow the standard daily dose recommendations? The answer is not clear cut and requires consideration of the risk:benefit ratio of the clinical scenario at hand. Is this serum creatinine value stable, rising, or declining? Are you concerned about the risk of overdosing or underdosing this particular patient? Is the patient receiving the agent for a documented infection or is this an empiric regimen? The risk of underdosing antimicrobial agents often outweighs the risk of overdosing and can be mitigated through therapeutic drug monitoring (TDM). In the absence of TDM, pharmacologic biomarkers, or easily measurable responses, the selection of the maintenance dose in an obese individual is left to clinical intuition.

In the case of an ABSSSI such as cellulitis, a lack of clear early response within 48 to 72 hours of therapy would prompt clinical consideration of the use of higher maintenance dose or an alternate agent. As an example, selection of a regimen of linezolid 600 mg every 8 hours is reasonable if an obese adult does not appear to be responding after 48 hours of therapy at an acceptable rate with the standard regimen of 600 mg every 12 hours. Similarly, selection of higher weight–based regimens of agents such as daptomycin will in theory lead to higher exposures in obese patients.[40] Recent data suggest that the CL of daptomycin may be augmented

and return to baseline over time in the critically ill.[41,42] A temporal physiologic phenomenon would imply that the maintenance dose should be temporarily increased for the first 72 to 96 hours and then returned to normal doses after this period.[41,42] Evaluation of this titrated maintenance dosing strategy is difficult to study prospectively especially when TDM is not available to guide this off-label consideration. However, in the age of "precision medicine," antimicrobial dosing beyond body size and kidney function estimates has to be explored.

ANTIMICROBIAL DOSAGE RECOMMENDATIONS IN OBESITY

Obesity is presently not recognized by regulatory bodies as a "special population" such as pregnancy, age, sex, renal, and hepatic impairment to mandate early-phase PK studies.[22] Several Phase III studies for newer agents against MRSA have included obese participants, but these post hoc findings are unlikely to motivate industry-supported changes to their drug label. Poor outcomes (safety profile or efficacy) in this population may not be apparent until the antimicrobial agent is used in the general population of obese patients. Product label recommendations for dosing of these newer agents in obesity only exist for daptomycin, whereby no specific adjustment for obesity is recommended. Several reviews exist in the literature on the dosing of drugs in obesity, including specific reviews on antimicrobial agents.[43–45] Over the past decade, specific studies have been performed to characterize the PK properties of antimicrobial agents in this population. These studies have involved the evaluation of small cohorts of healthy volunteers and have in large part supported and in some cases challenged the existing dosing paradigm. Whether these studies are sufficient to be translatable from healthy obese volunteers to infected obese patients is unclear. The next sections constitute a synopsis of evidence for key antimicrobial agents used to treat MRSA-related ABSSSIs.

INTRAVENOUSLY ADMINISTERED AGENTS

Vancomycin

The typical dosage of vancomycin in clinical trials of ABSSSIs has been 1 g or 15 mg/kg IV every 12 hours.[46] The V_d of vancomycin is larger than plasma volume and is similar to the estimate of total body water. Several PK studies have been performed with vancomycin in patients with obesity.[47–49] In addition, population PK models have included patients across a wide TBW range.[50] These studies found that the V_d of vancomycin correlates with TBW and that CL of this agent correlates with eCLcr but not in a proportionate manner.[50] In addition, vancomycin is considered an antimicrobial agent with time-dependent PK-PD properties in vitro, but validation of this parameter is not plausible clinically. The typical target trough of this agent was 5 to 10 mg/L when TDM was implemented for this agent and is now 10 to 20 mg/L. Because the MIC_{90} of MRSA is ≤ 2 mg/L, current and past dosing regimens lead to a 100% $T_{>MIC}$ in almost all patients when the trough is ≥ 5 mg/L, which limits (no spread) correlation of this PK-PD parameter to outcome. This point holds true even when free concentrations of vancomycin are considered. Studies also found a relation between vancomycin AUC:MIC with effect, and trough concentrations with toxicity. In practice today, trough concentrations are measured clinically as a surrogate of the AUC that provides the opportunity to tailor the dose of this agent in obese patients.[51]

Initial dosage recommendations, including those that are based on TBW, may be higher than necessary in obese patients but in essence guarantee achievement of concentrations considered therapeutic. TDM permits adjustment of the dosage of vancomycin within 48 hours of initiation in most obese patients.[23] Innovative Bayesian and practical approaches to compute the "right" dose have been developed and should be applied.[51] An empiric strategy of a 2-g loading dose followed by 1.5 g IV every 8 to 12 hours in obese patients (>100 kg) with normal kidney function is a reasonable starting point when managing ABSSSIs. This uncertainty is temporary because the dose can be modified after TDM is performed. The information gained from two point measurements (peak and trough) will be much more valuable in an obese patient than trough-only measurement.[52] This is because standard population estimates of vancomycin V_d are not reliable in this population that leads to less accurate estimates of AUC.[49,52] This information gained from vancomycin could be used to tailor other drugs such as daptomycin dosing in the extremely obese.[53] However, a systematic evaluation of this approach has not been performed because TDM is not readily available for other agents.

Daptomycin

Daptomycin is a relatively high protein bound (90%) lipopeptide that has a V_d that matches total plasma volume (5–10 L), inferring excellent concentrations for bloodstream infections but limited tissue distribution.[20] The PK profile of daptomycin has been studied in obesity, and population PK models have included individuals across a wide TBW range.[20,54,55] The interindividual variability in daptomycin PK parameters is relatively narrow compared with agents such as linezolid.[20,56] The correlation between daptomycin CL and body size is weak, and the population PK model for this agent includes eCLcr (capped at 150 mL/min) but not weight.[20] The justification for weight-based dosing of this agent is weak and the clinical uses of higher weight doses (8–10 mg/kg) for serious infections have limited supportive evidence beyond those of expert opinion. Consideration of LBW has been suggested when TBW is $\geq$111 kg but risks the computation of significantly lower doses than the use of AdjBW (Figure 3).[21] An obese patient of average stature (66 inches) will have to exceed approximately 220 kg in TBW before a daptomycin dose $>$500 mg would be computed using AdjBW (4 mg/kg). Finally, the use of IBW-based dosing has also been suggested but will lead to computation of lower doses than those tested in clinical trials, which may carry the theoretical but grave risk of the emergence of resistance.[57]

Ceftaroline

Ceftaroline is administered intravenously in its prodrug form, ceftaroline fosamil. The population PK profile of ceftaroline has been thoroughly evaluated, and the final model incorporated major shifts in CL and V_d (central) to explain the profile of patients with ABSSSI relative to healthy volunteers.[58] When considering the typical value of CL (11.6 L/h), this value increased by 35% in patients with ABSSSI compared with healthy volunteers. The typical value of the central V_d was 81% higher in patients with ABSSSI than healthy volunteers.[58] The relatively higher shift in the central V_d relative to CL is beneficial for time-dependent antimicrobial agents due to an extension in the half-life of the compound.[16] Body size parameters were found to also affect the central V_d and CL but did not reach the necessary level of significance to be retained in the final model.[58] An independent intensively sampled study of the pharmacokinetics of ceftaroline was performed in healthy volunteers across the BMI strata with a TBW range of 50.1 to 180 kg. Similar to the population model, eCLcr predicted ceftaroline CL, and TBW predicted V_d.[59] However, the net effects of these relations were no predicted alteration in the probability of target attainment for this agent. These data suggest that dosage adjustment of ceftaroline is not needed in obese patients. Importantly, analyses of a large dataset from a ceftaroline use registry have not identified lower response rates in obese patients with ABSSSI.

Telavancin

The risk:benefit ratio for consideration of telavancin is high relative to other available agents to MRSA-related ABSSSI.[9] This risk is particularly compounded in obese patients due to the recommendation for 10-mg/kg dosing based on TBW that exists for this agent.[60] Similar to daptomycin, the CL of telavancin is predicted by eCLcr and not TBW, implying that higher exposures would be expected in obese patients when dosed on TBW in groups with similar eCLcr.[61] Clinical trials that compared telavancin with vancomycin found higher rates of nephrotoxicity with this agent.[62] In addition, lower rates of efficacy have been documented in patients with reduced kidney function and a risk evaluation and mitigation strategy mandated by the Food and Drug Administration is required in women for childbearing potential due to risks of teratogenicity.[61] A clinical trial is currently under way to better define the dosing strategy of this agent in obese patients (NCT 02753855). As in the case above, use of a 7.5-mg/kg dose on TBW or the standard 10 mg/kg on AdjBW would limit the total daily dose to 1 g in obese patients $<$133 kg. Note that dose modification of telavancin is based on the Cockcroft-Gault equation and the use of IBW (not TBW).[60,61] Lower CLcr estimates will be consistently expected with use of IBW compared with TBW in obese patients. This distinction is important to remember, given the higher nephrotoxic potential of this compound relative to vancomycin.[9]

Oritavancin

Oritavancin is an intravenous antimicrobial agent that has been fully vetted across multiple dosing paradigms of weight-based, fixed dosing and as a large single dose.[62–65] The current approved single dose of 1200 mg takes advantage of very low systemic CL that

contributes to a large terminal half-life (245 hours).[65] Population PK analyses have included individuals across a wide weight spectrum (42.7–178 kg) across a BMI range of 15.9 to 67.4 kg/m^2.[65] The CL of oritavancin is predicted by height but is expected to only be 40% different between the two extremes of height studied in this model, an approximately 4 foot 2 inch and 6 foot 8 inch individual. This difference is expected to be <15% across most of the population (5–6 feet in height).[65] As a consequence, no dosage adjustment is expected with the use of oritavancin in adults. However, clinical experience regarding the safety profile of this single-dose agent is limited in obese patients who may require repeated dosing due to recurrence of ABSSSIs over time.

Dalbavancin

Dalbavancin is an intravenous antimicrobial agent recently approved to treat ABSSSI with a 2-dose regimen. A clinical trial comparing the single-dose regimen (1500 mg) with the 2-dose regimen (1000 mg, followed by 500 mg a week later) was completed and was found to be noninferior.[66] This regulatory-approved fixed-dose treatment regimen is supported by population PK analyses conducted in a large sample (n = 532) of adults with a wide distribution of weight (42.8–320 kg), BSA (1.36–4.00 m^2), and eCLcr (26–436 mL/min).[67] Both BSA and eCLcr were identified as covariates predictive of dalbavancin CL, whereas BSA was predictive of the central V_d. From this published population PK model, the concentration–time profile of dalbavancin (2-dose regimen) can be simulated to represent individuals with a body size of 75 kg (1.91 m^2), 150 kg (2.70 m^2), and 225 kg (3.31 m^2) and 175 cm in height (Figure 4). An assumption of 42 years and 1 mg/dL were selected for age and serum creatinine, respectively. Because PK system parameters are related to BSA, larger individuals will have lower C_{max} and AUC values. However, the $AUC_{0–336}$ is projected to be only 0.33-fold lower in the 225-kg individual relative to the 75-kg individual despite a 3-fold difference in weight. Similar to oritavancin, clinical experience with this agent remains limited to inform any concerns at this stage about dosing this agent in obese patients.

Tigecycline

Tigecycline, like other tetracycline derivatives, has a very large V_d (low plasma concentrations) and long half-life. The use of initial loading doses of 100 mg, followed by 50 mg IV twice daily, is designed due to this pharmacologic profile.[68] Higher doses of this agent have been studied but are associated with an exposure-related risk of nausea and vomiting.[69] In addition, the PK profile of tigecycline is unaltered in morbidly obese patients relative to nonobese patients to justify the need for higher doses to treat MRSA-related ABSSSI.[70] Irrespective, the existing black box warning for an increased risk in "all-cause mortality" relative to comparator agents relegates tigecycline to the end of the line within current treatment options.[9]

ORAL AND INTRAVENOUS-ADMINISTERED AGENTS

Linezolid

Linezolid is the first 100% bioavailable MRSA active oral agent to be available through a generic manufacturer.[71] This major cost reduction is likely to increase use of this agent relative to the more expensive and complex to administer intravenous agents. The PK profile of linezolid has been studied across a wide weight distribution and has included independent studies in obese subjects. Population PK analyses based on sparse sample data have found large interindividual variability in the system parameters of linezolid.[56] Studies directed at morbidly obese compared with lower BMI strata reported similar AUC values between cohorts.[72] Importantly, the V_d of linezolid has been found to be correlated with TBW, and a larger initial dose may be necessary with the first dose.[72] This relation has also been documented in a small cohort of bariatric patients who have served as their own controls after weight loss.[73] Time-dependent inhibition of linezolid metabolism has also been suggested that implies higher exposure of this agent than would be expected through simple linear translation of the data derived from single doses.[74] The implication of these studies is that a loading dose (50% higher than maintenance) may be necessary to achieve bioequivalent C_{max} and AUC exposures during the initial phase of therapy. However, given that the PK-PD profile of this agent is time dependent, modifying the current maintenance dose is unlikely to be necessary unless TDM is performed to justify this change.

Tedizolid

Tedizolid is an oxazolidinone agent approved for a short-course (6-day) treatment of ABSSSI in direct comparison with linezolid in clinical trials.[75] Tedizolid

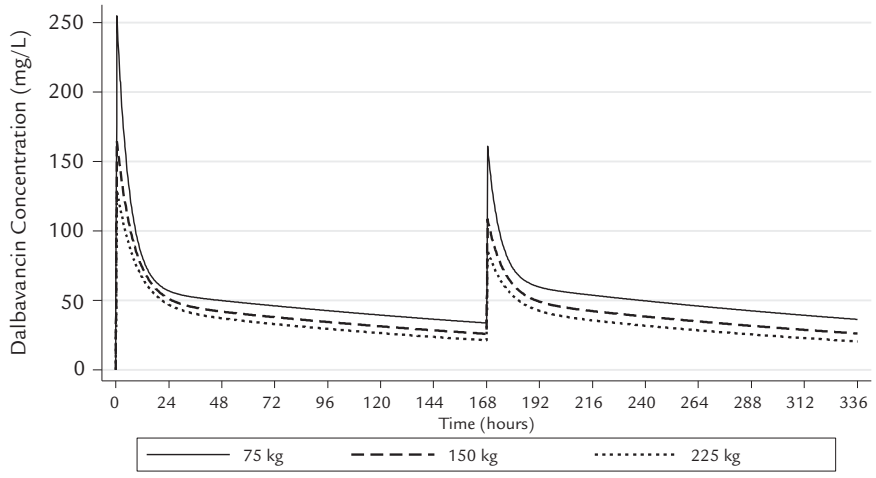

Figure 4. Simulated dalbavancin systemic concentrations in 3 individuals across a 3-fold weight range, illustrating higher maximum concentrations in smaller individuals but relatively similar concentrations 24 hours after the dose. The figure illustrates higher maximum concentrations in smaller individuals but relatively similar concentrations 24 hours after the dose.

has unique pharmacologic features to linezolid that permit single daily dosage, and it does not share the same risk as linezolid for serotonin syndrome when combined with certain antidepressants.[75] Population PK analyses found that the system parameters of tedizolid scale as a function of IBW and indicate that no dosage adjustment is necessary for body size.[76] A recent independent study confirmed that the tedizolid plasma PK profile is not significantly different in morbidly obese subjects compared with age-, sex-, and IBW-matched nonobese subjects.[77] These findings are relevant because lower numerical but nonsignificant trends in response rates were observed as a function of increasing BMI category in the pooled analyses of Phase III studies of tedizolid.[78] Despite these trends, insufficient evidence currently exists to recommend a higher daily dose of tedizolid in obese patients.

CONCLUSIONS

Several antimicrobial agents currently exist to manage ABSSSI secondary to MRSA. The dosing of these agents includes fixed and weight-based regimens. However, most product labels do not provide specific guidance for antimicrobial dosing in obesity. This deficiency can be problematic, given the high and increasing proportion of adults with obesity. Select drugs such as daptomycin and telavancin that are dosed on weight will lead to higher exposures in morbidly obese individuals when dosed on TBW that raise safety profile concerns. Uses of alternate body size descriptors such as AdjBW, a lower dose of milligram per kilogram, or capping the dose are potential solutions to manage this overdose concern. Other fixed-dose agents such as ceftaroline, oritavancin, dalbavancin, tigecycline, and tedizolid found correlations between their PK system parameters and body size, but the net PK-PD effects are insufficient to warrant dosage adjustment. Higher initial doses of linezolid may be warranted, and justification for higher maintenance doses could be supported with TDM because of high interindividual variability in the exposure of this agent. Similarly, initial dosage of vancomycin on TBW is reasonable to achieve target exposures, but a fixed-maintenance dosage regimen coupled with TDM is a practical pathway to dosing this agent in obese patients.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The author has indicated that he has no conflicts of interest regarding the content of this article.

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