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Optimization of Antibiotic Therapy in the Obese, Critically Ill Patient

Optimisation de l'antibiothérapie chez le patient obèse en réanimation

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Abstract As the prevalence of obesity increases worldwide, clinicians will be more and more frequently confronted with obese, critically ill patients. Optimal administration of antibiotics is already a challenge in the critically ill patient because pharmacokinetics (PK) of antibiotics is often altered, and infections are more frequently caused by resistant pathogens than in the non-critically ill patient. Obesity per se may further alter the PK of antibiotics. This paper provides a narrative review of the potential PK changes of antibiotics in the obese, critically ill patient, and recommendations for optimal antibiotic therapy for the most frequently used antibiotics. However, these recommendations are essentially based on small sample-sized PK studies with no evaluation of outcome, and thus must be considered with caution. On one hand, critically ill patients may need higher than recommended regimens of β-lactams, linezolid, moxifloxacin, levofloxacin, tigecycline, and colistin; however, no further dose adjustment is necessary in obese, septic patients. Increased dosage regimens of β-lactams may be necessary only to treat obese, non-critically ill patients. On the opposite, dosage regimens should be based on total body weight for amikacin in patients with a body mass index (BMI) between 20 and 40 kg/m^2, vancomycin, and daptomycin, and on adjusted body weight for ciprofloxacin, gentamycin, tobramycin, and amikacin in patients with a BMI greater than 40 kg/m^2. Because of the lack of PK studies in this special patient population, and the large inter- and intra-individual PK drug variability in critically ill patients, we recommend therapeutic drug monitoring of all antibiotics administered, whenever possible, to optimize drug therapy.

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Résumé Comme la prévalence de l'obésité augmente dans le monde, le clinicien sera de plus en plus fréquemment confronté à des patients obèses en réanimation. Il est particulièrement difficile d'administrer des antibiotiques de façon optimale à ces patients, car la pharmacocinétique (PK) de ces médicaments est souvent altérée et les infections sont plus souvent dues à des bactéries multirésistantes que chez des patients en dehors des services de réanimation. L'obésité est un facteur supplémentaire, qui pourrait modifier la PK des antibiotiques. Cette mise au point discute des altérations PK des antibiotiques possibles chez l'individu obèse en réanimation et propose des recommandations susceptibles d'optimiser leur administration dans ce contexte. Néanmoins, ces recommandations sont fondées sur peu d'études, souvent de petite taille et qui n'évaluent pas l'impact clinique. Elles doivent être considérées avec prudence. S'il faut préconiser l'usage de doses plus importantes de β-lactames, linézolide, moxifloxacine, lévofloxacine, tigécycline et colistine chez le patient en état critique, l'obésité ne va pas modifier pour autant cette stratégie thérapeutique. Des doses plus élevées que chez le patient non obèse sont nécessaires pour les β-lactames en cas de traitement d'infections non compliquées. Les doses se fondent sur le poids total du patient pour la vancomycine, le daptomycine et l'amikacine quand l'indice de masse corporelle (IMC) est compris entre 20–40 kg/m^2. Elles se fondent sur le poids ajusté pour la ciprofloxacine, la gentamicine, la tobramycine et l'amikacine si l'IMC est supérieur 40 kg/m^2. Puisqu'il y a une paucité des études de PK des antibiotiques chez les patients obèses en état critique et que les patients en réanimation présentent une variabilité PK inter- et intra-individuelle importante, on recommande, si possible, de faire un monitorage thérapeutique de tout antibiotique administré pour optimiser l'antibiothérapie.

Mots clés Obésité · Réanimation · Antibiothérapie · β-lactames

Introduction

The World Health Organization declared obesity, defined as a body mass index (BMI) greater or equal to 30 kg/m^2, a worldwide epidemic in 1997 [1]. Despite efforts to curb this problem, currently, in the United States of America, more than one third of adults and 17% of children are obese [2]. In Europe, between 10 and 30% of adults are obese and 33% of children are over-weight [3]. In developing countries, obesity is also on the rise [4].

The obesity epidemic is of great public health concern because obese individuals have a higher risk of morbidity and mortality for both acute and chronic health conditions than non-obese individuals [5]. Obesity is a risk factor for acquiring infections (community- or hospital-acquired) or for hospital and intensive care unit (ICU) admissions [6–9]. Furthermore, hospital stays are longer than in normal-weight individuals [9].

Vincent et al. showed in a multicentric point-prevalence study (EPIC II) carried out in 2007 that 71% of the 13,796 ICU patients included in this cohort were receiving antibiotic therapy [10]. The obese, critically ill patient is thus at high risk of needing antibiotic therapy when admitted to the ICU. In order to deliver optimal treatment and thus reduce mortality, rapid adequate antibiotic therapy needs to be given in life-threatening infections. Adequate therapy means that the antibiotic chosen should be active against the pathogen (s) responsible for the infection and that the dosage regimen should allow for the antibiotic concentration to be sufficient to treat the pathogen at the site of the infection in a timely fashion [11].

However, adequate antibiotic therapy to the critically ill patient is an important challenge for clinicians, as infections in the ICU are frequently caused by multidrug-resistant bacteria [9], and drug pharmacokinetics (PK) are often altered due to changes in the volume of distribution (VD) and total body clearance (CL) of drugs [12,13]. These PK changes may be further complicated with the more and more frequent use of extra-corporeal circuits [14]. Indeed, several papers have shown that standard dosage regimens of antibiotics result in inadequate serum concentrations in the critically ill patient to treat less susceptible strains; higher than recommended dosage regimens are then often necessary to optimize treatment in this patient population [15–18].

The PK of drugs may be even further altered in the obese, critically ill patient. As there is an absence of guidelines on how to optimize antibacterial delivery in obese, critically ill patients, the purpose of this article was to perform a narrative review of the potential PK changes of different antibiotics and to provide dose recommendations for these patients. We will only concentrate on antibiotics for which there is some clinical data, such as β-lactams, aminoglycosides, glycopeptides, fluoroquinolones, oxazolidinone, polymyxines, glycyclines, and lipopeptides.

Pharmacodynamic targets of antibiotics

When talking about optimizing antibiotic therapy, it is important to introduce some concepts on PK/pharmacodynamics (PD) of drugs. The PK of a drug is the study of the relationship between the dose administered and the concentration of the drug observed over time in the body fluids (i.e. essentially blood compartment) and tissues. Drug concentrations that are commonly used to describe antibiotic PKs are the trough concentration (C_{min}, i.e. the minimal concentration before the next dose), the peak concentration (C_{max}, i.e. the maximal concentration after a bolus administration), and the air under the concentration time curve (AUC). Pharmacodynamics is the study of the *in vivo* effect that the antibiotic has at a given concentration to kill or to inhibit the growth of bacteria. The minimal inhibitory concentration (MIC) is the minimal antibiotic concentration that results in the inhibition of the bacterial growth under standard conditions and is commonly used to quantify the pathogen's response to the antibiotic. Thus, PK/PD is the relationship between dose and effect. The following PK/PD parameters can be used to describe the efficacy of an antibiotic:

- for time-dependent antibiotics: the time that the serum concentration of the free fraction of the antibiotic remains above the MIC (fT > MIC);
- for concentration-dependent antibiotics: the ratio of the peak concentration to the MIC (C_{max}/MIC) during one dosing interval;
- and for concentration-dependent antibiotics with time dependency: the ratio of the AUC of the free fraction of the antibiotic from 0–24 h to the MIC ($AUC_{0\text{-}24}$/MIC), as shown in Fig. 1. The efficacy of each antibiotic will be best described by a specific PK/PD index. Specific PD targets have been identified for most antibiotics to ensure optimal efficacy [19].

Possible PK drug changes in obese patients

Obesity is *per se* associated with physiological changes that could theoretically alter the PK of antibiotics. The PK changes could be due to changes in drug absorption, distribution, or elimination.

Absorption

Absorption could be altered if antibiotics are administered orally or intra-muscularly [20,21]; as this review will focus

on critically ill patients, these ways of administration will not be explored in details. Moreover, absorption of intravenously administered antibiotics is not altered in this setting.

Drug distribution

Once absorbed, the antibiotic will distribute to the different tissues in the body. The extent of the distribution will depend on the lipophilicity, the hydrophilicity, protein binding, and the molecular weight of the antibiotic. Table 1 provides a classification of antibiotics with regard to their hydrophilic or lipophilic properties. The theoretical volume in which the antibiotic distributes is the VD. When the VD is small, as is the case with hydrophilic drugs, the drug is concentrated in the plasma, while when the VD is high, as is the case with lipophilic drugs, the drug distributes extensively to tissues. The VD of antibiotics in obese patients may be increased due to increased adipose tissue (composed of 30% water) [22], and to increased lean mass which may account for 20–40% of the patient's excess total body weight (TBW) [23].

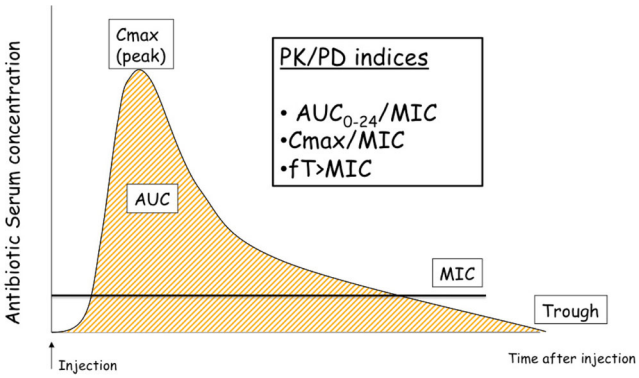

Fig. 1 Pharmacokinetics (PK)/pharmacodynamics (PD) indices that describe efficacy of antimicrobials. C_{max} = peak concentration; MIC = minimal inhibitory concentration; fT > MIC = time that the unbound drug exceeds the MIC of the pathogen; AUC = area under the curve

The VD may be further altered in the obese individual due to altered protein binding of the antibiotic caused by the increased levels of α_1-acid glycoprotein, cholesterol, triglycerides, or free fatty acids in the serum [24–26]. These serum components may increase or decrease protein binding by directly binding to the antibiotic, or by displacing or preventing the antibiotic to bind to serum proteins. Indeed, Morita and Yamaji observed a significant positive correlation between α_1-acid glycoprotein levels and protein binding of vancomycin [27]. Furthermore, Suh et al. showed in an *in-vitro* study that high levels of free fatty acids significantly decreased protein binding of cefamandole, dicloxacillin, and sulfamethoxazole, but increased protein binding of benzylpenicillin, cephalothin, and cefoxitin [28].

Table 1 Physical properties, PK/PD indices, and PD targets of antibiotics

Physical properties of antibiotics	PK characteristics	Antibiotics	PK/PD for efficacy	PD targets
Hydrophilic	Small VD Low intracellular and tissue penetration Essentially cleared by the kidney	β-lactams Aminoglycosides Glycopeptides Colistine	fT > MIC C_{max}/MIC AUC_{0-24}/MIC AUC_{0-24}/MIC	*Severe sepsis or septic shock* fT > 4–5 × MIC for 50–100% of the time *Other infections* fT > MIC for >40% of the time C_{max}/MIC > 8–10 AUC_{0-24}/MIC > 400 Unknown
Lipophilic	Large VD High intracellular and tissue penetration Essentially metabolized by the liver	Fluoroquinolones Linezolid Tigecycline	AUC_{0-24}/MIC or C_{max}/MIC AUC_{0-24}/MIC AUC_{0-24}/MIC	AUC_{0-24}/MIC > 125 C_{max}/MIC > 10 AUC_{0-24}/MIC of 80–120 *Skin infections* AUC_{0-24}/MIC > 17.9 *Complicated abdominal infections* AUC_{0-24}/MIC > 6.96
Other	—	Daptomycin	C_{max}/MIC AUC_{0-24}/MIC	AUC_{0-24}/MIC > 600

PK/PD = pharmacokinetic/pharmacodynamic; VD = volume of distribution; fT > MIC = time that the free fraction or unbound fraction of the antibiotic remains above the minimal inhibition concentration (MIC); C_{max} = peak concentration; AUC_{0-24} = air under the time curve during 24 h.

Finally, the VD may also be altered by blood flow to tissues. More specifically, studies on cefazolin and ciprofloxacin have suggested that obese patients may have poor peripheral perfusion, resulting in lower subcutaneous adipose tissue blood flow [29,30] and thus poorer distribution of antibiotics to subcutaneous tissues than in non-obese individuals [31,32]. On the contrary, enhanced subcutaneous blood flow in healthy, non-obese volunteers has resulted in higher subcutaneous ciprofloxacin concentrations [33].

Drug clearance

Lipophilic drugs are essentially metabolized by the liver. Obese patients are at risk of having hepatic steatosis or cirrhosis due to fatty infiltration, and thus diminished hepatic metabolism [34]. On the other hand, obesity can increase or decrease the activity of certain enzymes, such as cytochrome P450, which are responsible for phase I oxidative metabolism [35,36]. Furthermore, phase II reactions (conjugation by sulfation or glucoronidation) appear to be increased in obese individuals [37]. Little is however known concerning the global effect that obesity has on hepatic metabolism, and more particularly on the metabolism of antibiotics. Moreover, the obese, critically ill patient, like other ICU patients, is at risk of moderate acute liver failure due to global hypoperfusion or to a direct toxic effect on hepatic cells [38,39]. The half-life of antibiotics metabolized by the liver, such as ofloxacin and tigecycline, may increase under these conditions. The half-life of ofloxacin is increased 1.7 times and the half-life of tigecycline is increased by several hours (e.g. 18.7 h in healthy volunteers to 26.8 h) in patients with severe hepatic impairment [40]. However, clearance of other fluoroquinolones such as moxifloxacin [41], and ciprofloxacin [42] do not appear to be significantly altered in patients with severe hepatic impairment.

Hydrophilic drugs are only marginally affected by acute liver failure, as these drugs are essentially eliminated by the kidneys [43]. Renal clearance is increased in obese individuals due to increased cardiac output, total blood volume, and regional blood flow, but the increase is not proportional to the over-weight [44]. Furthermore, augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) more than or equal to 130 mL/min/1.73 m^2, refers to enhanced renal elimination of hydrophilic solutes, and has been clearly associated with subtherapeutic serum levels of antibiotics [45], and worse clinical outcomes in critically ill patients receiving standard doses of antimicrobial therapy [46]. ARC has been described in the obese, non-critically ill patient [47], and it is a common finding in critically ill patients with normal plasma creatinine concentrations [48]. On the other hand, many obese patients have co-morbidities such as arterial hypertension, and diabetes; renal insufficiency can therefore also be observed frequently in this population [49]. Furthermore, acute kidney injury is also a frequent complication observed in the critically ill patient [50,51] and may result in antibiotic accumulation. Moreover, when continuous renal replacement therapy (CRRT) is initiated in these patients, drug PKs could be even more altered. One important issue is that, although guidelines underline the importance of CRRT dose or intensity (i.e. at least 20–25 mL/kg/h of dialysis and/or ultrafiltration should be delivered) in critically ill patients, total CRRT dose is often suboptimal in the obese patient undergoing this therapy because of the difficulties to adjust dialysis/ultrafiltration rates to the weight of such patient; this could reduce the expected CRRT clearance of several drugs [52].

Theoretical antibiotic dosage adjustments

Based on size descriptors

The BMI is the most commonly used size descriptor for obesity. However, it does not take into account sex, race [53], or extreme muscle mass [54]. There are other size descriptors that can also be used to describe the obese patient, as shown and defined in Table 2 [55]. These size descriptors could be used to adapt antibiotic dosage regimens in obese patients. For example, it is suggested that lipophilic drugs require TBW dosing because drugs distribute extensively in tissue. On the other hand, it is suggested that hydrophilic drugs require adjusted body weight (ABW) or ideal body weight (IBW) dosing because hydrophilic drugs do not distribute to all tissues [56,57]. However, supporting clinical evidence is lacking for many antibiotics, and no single size descriptor best correlates with the VD and CL of antibiotics (either lipophilic or hydrophilic) in the obese individual [55].

Based on liver function

Hepatic clearance of drugs is currently not measured in a routine fashion, and few dosage adjustments for altered hepatic clearance of the antibiotics discussed in this review have been proposed. No dose adjustments are warranted for moxifloxacin and ciprofloxacin [41,42], but 50% of the total daily dose of tigecycline should be given in case of severe hepatic impairment [40].

Based on renal function

Antibiotic dosage adjustments for renally eliminated antibiotics do exist for patients with renal insufficiency; knowing the patient's renal function is therefore essential. Several equations to estimate CrCl are at the clinician's disposition, but none are perfect. Several studies have shown that the standard Cockcroft-Gault equation [58] poorly estimates

Table 2 Different frequently used size descriptors for body size [55–57]

Size descriptor	Definition	Estimation equation
Total body weight (TBW)	The total or actual weight of the individual	Measured on a scale (kg)
Body mass index (BMI)	The most frequently used body descriptor	= Weight (kg)/Height (m^2)
Ideal body weight (IBW)	Describes what weight an individual (in function of their height and sex) should be to have the best equilibrium between weight and height	Males = 49.9 + (0.89 × (Height (cm) − 152.4) Females = 45.4 + (0.89 × (Height (cm) − 152.4)
Adjusted body weight (ABW)	IBW plus a proportion of the difference between TBW and IBW, otherwise known as the dosing weight correction factor (DWCF). The DWCF reflects that drugs will distribute differently to the excess adipose tissue	= DWCF × (TBW − IBW) + IBW
Body surface area (BSA)	Often used to calculate doses for chemotherapy	= $TBW^{0.425}$ × Height $(cm)^{0.725}$ × 0.007184
Lean body weight (LBW)	Body weight devoid of adipose tissue	Males = (9270 × TBW)/(6680 + (216 × BMI)) Females = (9270 × TBW)/(8780 + (244 × BMI))
Fat free mass (FFM)	Body tissues (muscle, bone, organs, and extracellular fluids) often measured by bioelectrical impedance analysis	Males = (TBW × 0.285) + (12.1 × Height $(m)^2$) Females = (TBW × 0.287) + (9.74 × Height $(m)^2$)

the renal function in obese individuals [59–61]. The Modification of Diet in Renal Disease (MDRD4) was developed based on data from patients with chronic renal insufficiency; however, the use of this equation in patients without renal disease may be inaccurate [62]. The Salazar-Corocan equation [63], and the Cockcroft-Gault equation calculated with ABW over-estimated CrCl. On the other hand, the Cockcroft-Gault equation calculated with lean body weight (LBW) yielded accurate estimates, but only in a small cohort of 54 morbidly obese patients [64]. Finally, the CrCl estimations obtained with the MDRD4, the Cockcroft-Gault, and the CKD-EPI [65] equations were compared with measured renal clearance in a group of potential obese kidney donors. All of the equations either over-estimated or under-estimated the glomerular filtration rate depending on the BMI of the patient [61]. Furthermore, none of these equations have been validated in the obese individual in the ICU setting.

Specific dose adjustments of antibiotics do not exist for patients with ARC, but it is essential to identify these patients in order to consider increasing antibiotic dosage regimens. However, no equation estimates accurately the renal function in the ICU patient with ARC [66]. Currently, 8–24 hour urine collects are the most precise and practical way to estimate the renal function in the obese, critically ill patient [45].

β-lactams

β-lactams, including penicillins, cephalosporines, and carbapenems, are time-dependent antibiotics. There is no consensus concerning the optimal PD target for β-lactams. However, for severe infections in critically ill patients, the PD target of fT > 4–5 × MIC for 50–100% of the time is probably optimal, and for less severe infections, fT > MIC for 40–100% of the time is probably sufficient [67]. In order to improve PD target attainment, the β-lactams can be administered with increased doses, increased frequency, and prolonged infusion or continuous infusion.

Several case reports and case series have shown that increased dosage regimens of β-lactams were needed to treat obese, septic and non-septic patients when dealing with difficult-to-treat pathogens such as *Pseudomonas aeruginosa* [47,68–70]. Moreover, Roberts et al. also showed that 25% of the 236 ICU patients (obese and non-obese) included in a proof of concept study on therapeutic drug monitoring (TDM) in the ICU needed increased dosage regimens of β-lactams to treat infections adequately [71]. Hites et al. also showed in a retrospective case-control study in obese, septic patients (median BMI of 40 kg/m^2) receiving β-lactam therapy that PK of drugs was no different in obese than non-obese patients, but that 30% of TDMs performed showed insufficient serum concentrations (T < 4 × MIC) to treat difficult-to-treat pathogens such as *P. aeruginosa*. They concluded that sepsis alone was responsible for the essential PK changes observed in obese, critically ill patients [52].

Several other PK studies have been carried out in obese individuals receiving cefepime, piperacillin-tazobactam, ertapenem, doripenem, and meropenem. Only studies on piperacillin-tazobactam, doripenem, and meropenem were performed in obese, critically ill patients. The study on cefepime was carried out in 10 obese patients undergoing

bariatric surgery (BMI ≥ 40 kg/m^2); patients were not infected, nor critically ill. Two grams every 8 h were sufficient to attain a PD target of fT > MIC during 60% of the dosage interval in 9/10 patients, but this dosage regimen was not sufficient to attain PD targets of fT > 4 × MIC during 50–100% of the dosing interval [72]. The study on ertapenem was also performed in healthy volunteers belonging to 3 different BMI groups. The VD was significantly greater in the more obese individuals compared with non-obese individuals, and PD target attainment, defined as a fT > MIC for 40% of the dosing interval, was very low in all groups of BMI when optimizing treatment to cover pathogens with MICs greater than 0.25 mg/L. Severely obese patients had lower PD target attainment than non-obese individuals [73]. The study on meropenem was carried out in 9 obese, critically ill patients. Two PD targets were explored; all drug regimens (even 500 mg every 6 h) achieved a PD target attainment of >90% when the PD target was fT > MIC for 40% of the dosing interval for very sensitive strains. However, when the PD target was fT > MIC for pathogens with an MIC of 2 mg/L (the clinical breakpoint for *P. aeruginosa*), only regimens of 1 g every 6 h infused over 30 min, and 2 g every 8 h achieved a PD target attainment of >90%. Results showed that PK parameters were similar to those observed in non-obese individuals, except for a bigger absolute VD, but smaller VD when normalized for weight [74]. The PK study on doripenem was carried out in 31 critically ill patients with nosocomial pneumonia, of varying weight (83 ± 19) and BMI (27.8 ± 6.3). The PD target was fT > MIC for 40% of the dosing interval. As TBW increased, the probability of PD target attainment decreased for pathogens with an MIC of 4 mg/L. Extended infusions of doripenem could improve antibiotic exposure and were then recommended in obese patients [75].

The PK study on piperacillin-tazobactam was carried out in 9 morbidly obese, critically ill patients. The PD target was fT > MIC for 50% of the dosing interval. All patients attained the PD target of fT > MIC for 100% of the dosing interval for infections due to pathogens with an MIC of 16 mg/L [76]. On the other hand, Cheatham et al. showed in a case series of 14 obese patients (7 hospitalized in the ICU) receiving piperacillin-tazobactam that higher dosage regimens were necessary to attain PD targets of fT > MIC for 50% of the dosing interval. VD was increased in obese individuals compared with non-obese individuals, but when normalized to TBW, VD was smaller. The probability for PD target attainment was calculated for different MICs. Larger doses were needed in obese patients to provide comparable PD exposures for pathogens with elevated MICs [77]. Similar results were obtained in a case series of obese, non-critically ill patients [47]. Furthermore, in patients treated with piperacillin-tazobactam for complicated intra-abdominal infections, the response rate was 86% for patients with a BMI < 30 kg/m^2, and only 65% for those with a BMI ≥ 30 kg/m^2 [78].

In conclusion, in severe sepsis and septic shock, PK of β-lactams does not appear to be different in obese and non-obese individuals. However, in less severe infections, obesity may be responsible for PK changes, with essentially increases in total VD and increase in CL. For infections due to pathogens with low MICs, dose adjustment for obesity is not necessary. However, for infections due to pathogens with higher MICs, prolonged infusions, or increased frequency of dose administration, may be necessary to ensure adequate PD target attainment. Table 3 shows some examples for dosage recommendations.

Aminoglycosides

Aminoglycosides, such as tobramycin, gentamycin, and amikacin, are concentration-dependent drugs and are administered essentially for suspicion of or confirmed severe gram-negative infections. Their accepted PD target is a C_{max}/MIC > 8–10 [66]. In order to attain this PD target in the critically ill patient, it is recommended to administer aminoglycosides based on a once-daily (or extended interval) dosage regimen, by giving a loading dose of 7–8 mg/kg for both tobramycin and gentamycin [79] and 25 mg/kg for amikacin [15], followed by further doses based on TDM. The TDM permits clinicians to diminish the risk of toxicity and to increase the chance of PD target attainment [67], otherwise difficult due to the great PK variability observed in critically ill patients; clinical estimates of parameters such as glomerular filtration can help to explain only about 50% of this variability [80].

When we consider the obese patient, studies have shown that the VD and CL of aminoglycosides are increased, but not proportionally to TBW [81]. Therefore, it has been historically widely accepted to adapt dosage regimens to ABW based on a correction factor of 0.4 [81]. However, the aminoglycoside correction factor can range from 0.14 to 0.98 [82]. Ross et al. provide the only PK data on morbidly obese patients having received a once-daily aminoglycoside regimen based on ABW. Indeed, 40 morbidly obese patients with serum creatinine levels of ≤1.5 mg/dl were included in this retrospective analysis of data on PK of gentamycin and tobramycin. No information concerning severity of infection or department where the patient was hospitalized was provided. Sixteen percent of patients had insufficient serum concentrations to treat infections due to less susceptible pathogens, such as *P. aeruginosa*. Despite these results, the authors advocated to pursue dosage regimens based on ABW in obese patients [83]. Pai et al. suggested that LBW is a better body size descriptor than ABW for adapting the dosage regimen in obese patients because when VD was indexed for LBW, VD remained constant for all strata of BMI, while when VD was indexed for TBW, it decreased

Table 3 Antibiotic dosage recommendations for obese, critically ill patients

Antibiotic		Dose recommendation
β-lactams	Severe Sepsis Septic Shock	No dose adjustment compared to non-obese individuals [52]
	Others	Increased dosage regimens with either prolonged infusions or increased total daily doses [72–75,77] Cefepime: 2 g in 3 h infusions every 8 h Piperacillin-tazobactam: 6.75 g in 4 h every 8 h Doripenem: 500 mg in 4 h infusions every 8 h Meropenem: 1 g every 6 h or 2 g every 8 h
Aminoglycosides	Gentamycin	Loading dose of 7–8 mg/kg based on ABW, followed by TDM-based dose adjustment [79,83]
	Tobramycin	Loading dose of 7–8 mg/kg based on ABW, followed by TDM-based dose adjustment [79,83]
	Amikacin	Loading dose: BMI < 40 kg/m^2: 25 mg/kg based on TBW, followed by TDM-based dose adjustment [15] BMI ≥ 40 kg/m^2: 30 mg/kg based on ABW or LBW, followed by TDM-based dose adjustment [80,83]
Glycopeptides	Vancomycin	Continuous infusion Loading dose: 35 mg/kg [86] based on TBW [87] Maintenance dose: based on measured CrCl and TBW [87]
Fluoroquinolones	Moxifloxacin	No dose adjustment [96]
	Levofloxacin	No dose adjustment [99] or dose adjustment (500 mg, 750 mg, 1000 mg, 1250 mg) stratified by CrCl obtained with the Cockcroft-Gault equation using IBW [101]
	Ciprofloxacin	Dose adjustment based on ABW with a DWCF of 0.45 [97]
Oxazolidinone	Linezolid	Consider giving an increased dosage regimen of 600 mg every 8 h for infections due to pathogens with an MIC of 4 mg/L or greater [105,108]
Polymyxines	Colistin	Loading dose of 6–9 MIU, followed by 4.5 MIU every 12 h [112] Loading dose: Colistin MIC target (mg/L) × 2.0 × IBW Maintenance dose: Colisitin MIC target (mg/L) × (1.50 × CrCl + 30) If CrCl < 10 ml/min/1.73 m^2: every 12 h, CrCl 10–70 ml/min/1.73 m^2: every 8 h CrCl > 70 ml/min/1.73 m^2: every 8 h, but little chance of attaining PD target [113]
Glycylines	Tigecycline	No dose adjustment, but high dose recommended: 100 mg every 12 h [117–119]
Lipopeptides	Daptomycin	Dosage regimens should be based on TBW. Higher dosage regimens of 8–12 mg/kg should be considered if severe gram-positive infection [122,123]

ABW = adjusted body weight; TDM = therapeutic drug monitoring; BMI = body mass index; TBW = total body weight; CrCl = creatinine clearance; DWCF = dosing weight correction factor; MIC = minimal inhibitory concentration; MIU = million international units; IBW = ideal body weight.

as BMI increased [80]. Dosage regimens based on LBW remains a convincing alternative, but awaits prospective validation.

On the other hand, Taccone et al. have suggested that dosage regimens of amikacin be based on TBW. Indeed, in a prospective study on 74 patients in severe sepsis or septic shock, 79% of patients would have attained the PD target of >64 mg/L when delivering a dose of 30 mg/kg based on TBW, compared with 56% when delivering a dose of 25 mg/kg based on ABW (calculated when BMI was >28 kg/m^2). However, patients with a BMI > 40 kg/m^2 were excluded from this study [15]. Therefore, aminoglycoside dosing should be based on TBW for BMI varying from 20 to 40 kg/m^2. When BMI is ≥40 kg/m^2, ABW or LBW should be used to determine the dosage regimen, followed by TDM-based dosage adjustment (Table 3).

Glycopeptides

Glycopeptides, such as vancomycin, are concentration dependent with time-dependent drugs used to treat gram-positive infections. The accepted PD target is $AUC_{0\text{-}24}$/MIC > 400. For intermittent dosing, a trough concentration of 15 mg/L will result in an $AUC_{0\text{-}24}$/MIC > 400 for *Staphylococcus aureus* with an MIC of 1 mg/L; when the drug is given as a continuous infusion, a steady-state concentration of 25 mg/L will result in an $AUC_{0\text{-}24}$/MIC > 400 in pathogens with an MIC of 1.5 mg/L [67]. Although both regimens can be administered in the ICU, continuous infusion offers the following advantages: faster acquisition of target concentrations, fewer samples per treatment to monitor vancomycin concentrations in serum, less variability in the daily given dose, less expensive, and significantly lower risk of drug-related nephrotoxicity when the same daily dosage regimens are administered [84,85]. Roberts et al. have proposed a dosage regimen for the critically ill patient to enable rapid PD target attainment: loading dose of 30–35 mg/kg, followed by maintenance doses adjusted on CrCl (i.e. 35 mg/kg/24 h for patients with CrCl > 80–100 ml/min/1.73 m^2 [86]. However, this dosage regimen still needs validation in a prospective study.

The CL and VD of vancomycin are increased in obese patients, and they correlate best with TBW [87–89]. Thus it is suggested that the loading and maintenance dose be calculated based on TBW. The maintenance dose needs to be guided by measured CrCl, but also by TDM performed on the second day of therapy. Because dosage regimens based on TBW are advocated, obese individuals will inevitably receive large daily doses of vancomycin. Lodise et al. showed in a retrospective study on 332 randomly selected patients that large vancomycin doses (≥4 g/day), TBW ≥ 101.4 kg, hospitalization in the ICU, and estimated CrCl ≤ 86.6 ml/min were independently associated with time to nephrotoxicity [90]. However, other studies have failed to reach the same conclusions: only elevated vancomycin trough serum concentrations, duration of therapy, and intermittent therapy were independently associated with increased odds of nephrotoxicity [91–93]. Vancomycin dosage recommendations are shown in Table 3.

Fluroquinolones

Fluoroquinolones, such as levofloxacin, moxifloxacin, or ciprofloxacin, are concentration dependent with time-dependent antibiotics. Efficacy is best achieved when the $AUC_{0\text{-}24}$/MIC > 125 or C_{max}/MIC > 10 [93]. In critically ill patients, the recommended dosage regimen for ciprofloxacin, levofloxacin, and moxifloxacin are 400 mg every 8 h [18,94], 1 g every 24 h [95], and 400 mg every 24 h [96], respectively.

In obese individuals, the VD of ciprofloxacine is increased. A study by Allard et al. showed that by using ABW with a dosing weight correction factor (DWCF) of 0.45 to normalize the VD, no more differences were observed between obese and non-obese individuals. The authors concluded that dose adjustments should be made based on the ABW with a DWCF of 0.45 [97]. Utrup et al. then reported a case-report of a critically ill, severely morbidly obese patient with renal insufficiency that received 800 mg IV every 12 h of ciprofloxacin; the PD target was attained, as well as initial clinical and microbiological success [98]. Another study comparing a dose of 2.85 mg/kg of ciprofloxacin based on ABW in 12 obese subjects and 12 lean subjects showed that plasma concentrations were much greater in the obese patients, but that tissue concentrations were similar in the two groups. The authors concluded that dosing should be based on TBW, and not ABW [32].

On the other hand, in a study on levofloxacin given in 15 infected obese individuals, drug PKs were highly variable among patients, but overall they were similar to normal-weight individuals (historical controls taken from other studies) [99]. Indeed, Luque et al. also report the case of an obese patient (179 kg) treated with an adjusted dosage regimen of 750 mg IV every 12 h (based on the ABW with a DWCF of 0.45). The $AUC_{0\text{-}24}$/MIC obtained in that patient was double than the antibiotic exposure observed in non-obese healthy volunteers receiving 750 mg once daily. The authors suggested that levofloxacin dosage adjustment might not be necessary in obese individuals [100]. Also, Pai et al. evaluated results obtained from TDM monitoring of 68 severely morbidly obese individuals receiving levofloxacin; they concluded that dosage adjustment was necessary. They proposed an empiric 4-category daily-dose regimen (500 mg, 750 mg, 1000 mg, 1250 mg) stratified by an estimated CrCl using the Cockcroft-Gault equation based on IBW [101].

Finally, only one study on moxifloxacine has been carried out in obese patients. The PK results were compared with non-obese historical controls. No significant PK differences were found in the plasma, but concentrations in subcutaneous fat were lower in obese patients compared with non-obese patients. Nevertheless, the authors concluded that no dosing adjustments needed to be made for obese patients (Table 3) [96].

Oxazolidinones

Linezolid is concentration dependent with time-dependent antibiotics used to treat serious gram-positive infections. The PD target is $AUC_{0\text{-}24}$/MIC between 80 and 120 [67].

Several case reports have suggested that standard dosage regimens of linezolid in the obese patients do not allow for PD target attainment [102–104]. However, in a PK study of linezolid in healthy obese patients, the values of AUC_{0-24}/MIC were similar to historical non-obese controls [105]. Furthermore, despite that the PK of linezolid in ICU non-obese patients is altered with increased VD and increased non-renal clearance resulting in decreased drug exposition, linezolid provided high levels of clinical cure and microbiological success [106,107]. On the other hand, two PK studies in 12 and 5 critically ill patients suggested that serum concentrations obtained with the standard dosage regimen were too low to offer optimal antibiotic treatment in a subgroup of critically ill patients, therefore suggesting more frequent daily dosing for infections due to bacteria with an MIC of 4 mg/L [108,109]. As there are currently no PK studies in obese, critically ill patients, dosage recommendations should remain unchanged for infections due to bacteria with MICs ≤ 2 mg/L: 600 mg every 12 h (Table 4). However, for infections due to bacteria with MICs close to 4 mg/L, increased dosage regimens (i.e. 600 mg every 8 h) should be considered.

Polymyxines

Colistin, a metabolite of the prodrug colistimethate sodium (CMS), is an old drug, which has gained a recent interest as an alternative option to treat infections due to multidrug resistant gram-negative bacteria. The PK/PD index that best describes efficacy is AUC_{0-24}/MIC, although some controversies still remain [110]. Dosage regimens need to be expressed in international units (IU) because the amount of colistin in vials is different from one country to another, and certain vials refer to CMS while others to colistin. It is established that 1 mg of colistin base is equal to 30.000 IU and 1 mg of CMS is equal to 12.500 IU [110].

The standard dosage regimen of colistin in non-critically ill patients with normal renal function is 3 IU × 10^3 (MIU) every 8 h [110]. However, this dosage regimen appears to be inadequate in the critically ill patient because it takes 2–3 days to reach steady-state concentrations; moreover, even at the steady-state, serum concentrations of colistin were below the clinical breakpoints of 2 mg/L for *P. aeruginosa* and *Enterobacteriaceae* spp. [111–113]. Several dosing regimens have been recently proposed, including a loading dose of 6–9 MIU and a daily dose of 4.5 MIU given every 12 h [112,113]: however, clinical data validating such approach remain limited [114].

Dosage regimens need to be adapted to renal function, because in patients with renal failure, clearance of CMS and colistin is decreased while conversion of CMS to colistin and drug exposure is increased. Suggestions for dosage regimens in patients with renal failure have been proposed by Garonzik et al [113]. However, in this multicentric study in 105 critically ill patients, PD target attainment was virtually impossible for patients with a CrCL > 70 ml/min/1.73 m^2, when treating an infection due to a pathogen with an MIC of >0.5 mg/L for colistin [113].

Four PK studies dealing with colistin PK and weight have been carried out in the critically ill population. The first 3 smaller studies (n = 10; n = 14; n = 18) did not find any correlation between body size and VD of colistin, but inter-patient variations in weight were limited (median TBW of 80 (60–140) kg and only one patient having 140 kg [114]; median TBW of 80 (65–110) kg [111]; mean TBW of 72.5 ± 8.5 kg [112]). Another larger study with patients of varying weights (median TBW of 59.1 (30–106.4) kg) did show a correlation between IBW and VD of colistin, thus justifying the proposition of administering a loading dose based on IBW [113]. No correlation was found between CL of colistin and body size in any of the studies; therefore maintenance doses are not based on body size descriptors.

When prescribing colistin, particular attention must be paid on toxicity. A BMI > 31.5 kg/m^2 was identified as an independent risk factor for nephrotoxicity in patients receiving colistin therapy. The dosage regimen administered in mg/kg when considering TBW or IBW was not different in patients who developed renal toxicity compared with those who did not [115].

Aerosol administration of colistin (2 MIU) in critically ill patients with pneumonia in a small series of patients (n = 12) has revealed promising PK/PD results: concentrations of colistin in the epithelial lung fluid were higher than when CMS was administered intravenously [116]. Aerosol administration of colistine may be considered in obese, critically ill patients with pneumonia due to multidrug resistant gram-negative bacilli, especially when renal failure is present.

Glycylines

In the era of multidrug resistant gram-negative infections, tigecycline has found a place in the pharmacological arsenal of ICU physicians. The PK/PD index that best predicts efficacy of the drug is the AUC_{0-24}/MIC. The PD target for complicated skin infections and intra-abdominal infections is AUC_{0-24}/MIC > 17.9 and > 6.96, respectively [117]. Pai has shown in a PK study in healthy obese (n = 8) and non-obese (n = 4) volunteers that serum PK of tigecycline was similar in the two groups. However, the probability of PD target attainment for the treatment of gram-negative pathogens with the dosage regimen of 100 mg, followed by 50 mg BID, was very low, regardless of the body size of the individual [118]. Xie et al. showed that the probability of PD target attainment was 67% for infections due to pathogens

Table 4 Characteristics of the studies reporting on pharmacokinetics used for elaborating the dosage recommendations

Author, year [reference]	Study design, country	Number of patients	Drug regimens administered	Comparison with non-obese patients	PK/PD target	Conclusions
β-lactams						
Hites, 2013 [52]	Retrospective case-control, Belgium	49 obese patients 68 TDMs	MEM TZP CEFE CAZ	Yes (n = 59)	MEM: 8–16 mg/L during 40% of the dosing interval TZP: 64–128 mg/L during 50% of the dosing interval CAZ/CEFE: 32–64 mg/L during 70% of the dosing interval	No PK difference between obese and non-obese individuals in septic shock or severe sepsis
Rich, 2012 [72]	Prospective PK study, USA	10 morbidly obese patients undergoing bariatric surgery	CEFE (2 g one dose)	Yes (historical controls)	fT > MIC during 60% of the dosage interval and fT > 4 × MIC 50% of the dosing interval	Serum concentrations are lower in morbidly obese individuals than in non-obese individuals
Chen, 2006 [73]	Prospective PK study, USA	30 volunteers 10 patients in each BMI group: 18–25 kg/m^2, 30–39 kg/m^2, ≥40 kg/m^2	ERTA (1 g one dose)	Yes	fT > MIC during 40% of the dosing interval	Severely obese patients had lower PD target attainment than non-obese individuals
Cheatham, 2014 [74]	Prospective PK study, USA	9 morbidly obese MCS	MEM (500 mg/1 g q6h)	No	fT > MIC during 40% of the dosing interval	Standard doses achieve adequate PD target attainment
Roberts, 2013 [75]	Multicentric, PK Study, France	31 patients with nosocomial pneumonia, BMI: 22–34 kg/m^2, MCS	DORI (250/500 mg) 30 min bolus 1-h infusion 4-h infusion	Yes	fT > MIC during 40% of the dosing interval	As TBW increased, the probability of target attainment decreased for pathogens with an MIC of 4 mg/L or greater
Sturm, 2014 [76]	Prospective PK study, USA	9 morbidly obese	TZP (4.0/0.5 g q6h)	Yes (historical controls)	fT > MIC during 50% of the dosing interval	This dosage regimen achieved 100% PD target attainment for pathogens with an MIC of 16 mg/L or lower
Cheatham, 2013 [77]	Prospective PK study, USA	14 obese patients (7 critically ill), MCS	TZP (4.0/0.5 g q8h, 6.0/0.75 g q8h EI)	No (comparison with historical controls)	fT > MIC during 50% of the dosing interval	Larger doses of TZP were needed in obese patients to provide comparable PD exposures for pathogens with elevated MICs

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Table 4 *(suite)*

Author, year [reference]	Study design, country	Number of patients	Drug regimens administered	Comparison with non-obese patients	PK/PD target	Conclusions
Aminoglycosides						
Ross, 2013 [83]	Retrospective, USA	31 morbidly obese without renal failure	GENT/TOBR (5–7 mg/kg q24h) (Adjusted BW)	No	Serum concentration 16 h after dose administration: 0.5–2 mg/L	16% of patients had sub-therapeutic serum concentrations to treat infections due to less susceptible pathogens
Taccone, 2010 [15]	Prospective PK study, Belgium	74 patients in severe sepsis or septic shock	AMK (25 mg/kg) (TBW)	Yes	>8 times the MIC of the pathogen	Dosage regimens based on TBW permitted better PD target attainment than regimens based on adjusted body weight using a correction factor of 0.4
Pai, 2011 [80]	Prospective PK study, USA	497 treated with TOBR (91 obese) 1576 treated with GENT (298 obese)	Dosing regimen selected by physicians	Yes	—	Dosing should be based on LBW
Glycopeptides						
Roberts, 2011 [86]	Retrospective PK study, Belgium	206 MCS	Vancomycin: CI 15 mg/kg LD 30 mg/kg DD 30-35 mg/kg according to the TWB and renal function	No	—	New dosage regimen is proposed
Blouin, 1982 [87]	Prospective PK study, USA	6 morbidly obese 4 volunteers	Vancomycin (1 g one dose)	Yes	—	Higher CL and VD are observed in obese patients than in non-obese patients. Both CL and VD correlate well with TBW
Fluoroquinolones						
Kees, 2011 [96]	Prospective PK study, Germany	12 morbidly obese	Moxifloxacin (400 mg q24h)	Yes (historical controls)	—	Plasma PK was not different between obese and non-obese individuals. However, tissue concentrations were lower in obese patients

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Table 4 *(suite)*

Author, year [reference]	Study design, country	Number of patients	Drug regimens administered	Comparison with non-obese patients	PK/PD target	Conclusions
Cook, 2011 [99]	Prospective PK study, USA	15 obese	Levofloxacin (750 mg one dose)	Yes (historical controls)	—	AUC and CL of levofloxacin are variable in obese patients. Risk of under-dosing when using standard doses
Pai, 2014 [101]	Retrospective PK study, Italy	68 (BW = 98–250 kg)	Levofloxacin (750 mg q24h)	Yes	—	Dosage adjustment is necessary in obese patients
Allard, 1993 [97]	Prospective PK study, Canada	17 obese volunteers	Ciprofloxacine (400 mg one dose)	Yes	—	The VD is increased in obese subjects, but is normalized with ABW using a correction factor of 0.45. Dose adjustments should be based on ABW
Oxazolidinones						
Bhalodi, 2012 [105]	Prospective PK study, USA	20 obese volunteers	Linezolid (600 mg q12h)	Yes (historical controls)	—	No PK differences between obese and non-obese individuals (up until 150 kg)
Buerger, 2006 [108]	Prospective PK study, Austria	12 critically ill	Linezolid (600 mg q12h	No	—	More frequent administration of linezolid should be considered in critically ill patients
Polymyxines						
Plachouras, 2009, [112]	Prospective PK study, Greece	18 critically ill (BW = 65–110 kg)	Colistine (3 MU q8h)	No	—	Plasma concentrations are insufficient before steady state: a LD of 9–12 MU is proposed
Garonzik, 2011 [113]	Prospective PK study, USA/ Thailand	105 critically ill	Colistine	Yes	—	Dosage recommendations are provided. Correlation found between IBW and VD of colistin, but no correlation between CL and body size. Proposition of a loading dose based on IBW

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Table 4 *(suite)*

Author, year [reference]	Study design, country	Number of patients	Drug regimens administered	Comparison with non-obese patients	PK/PD target	Conclusions
Glycylines						
Xie, 2014 [117]	Case series PK study	MCS	Tigecycline (50 mg q12h, 100 mg q12h)	No	—	High dose (100 mg every 12 h) allows for a probability of PD target attainment of 67% due to pathogens with an MIC of 0.5 mg/L
De Pascale, 2014 [119]	Retrospective, Italy	100 critically ill	Tigecycline (50 mg q12h, 100 mg q12h)	No	—	High-dose tigecycline was well tolerated in critically ill patients
Pai, 2013 [118]	Prospective PK study, USA	8 morbidly obese volunteers	Tigecycline (100 mg)	Yes	—	No PK differences difference between obese and non-obese individuals; however, the probability of target attainment for treatment of gram-negative pathogens was very low for all body sizes
Lipopeptides						
Falcone, 2013 [122]	Prospective PK study, Italy	50 critically ill MCS	Daptomycin (6–8 mg/kg)	No	AUC_{0-24}/MIC > 666	Higher dosage regimens may be needed in critically ill patients
Dvorchik, 2005 [121]	Prospective PK study, USA	13 obese volunteers	Daptomycin (4 mg/kg) (TBW)	Yes		Exposure to Daptomycin was increased in the obese and morbidly obese subjects
Pai, 2007 [123]	Prospective PK study, USA	7 morbidly obese volunteers	Daptomycin (4 mg/kg) (TBW)	Yes		No PK differences between obese and non-obese individuals when AUC_{0-24} and C_{max} normalized to TBW

TDM = therapeutic drug monitoring; BMI= body mass index; PD = pharmacodynamics; PK = pharmacokinetics; fT = free fraction or unbound fraction of the antibiotic; fT > MIC = free or unbound fraction of the antibiotic greater than the minimal inhibitory concentration of the pathogen; MIC = minimal inhibitory concentration; AUC_{0-24}/MIC = ratio of the air under the curve during 24 h to the minimal inhibitory concentration of the pathogen; C_{max} = peak serum concentration; TBW = total body weight; IBW = ideal body weight; MEM = meropenem; CAZ = ceftazidime; CEFE = cefepime; TZP = piperacillin-tazobactam; ERTA = ertapenem; MCS = Monte Carlo Simulation; EI = extended infusion; BW = body weight; AMK = amikacin; GENT = gentamycin; TOBR = tobramycine; LBW = lean body weight; CI = continuous infusion; LD = loading dose; DD = daily dose.

with an MIC of 0.5 mg/L when a high dosage regimen of 100 mg was given twice a day [117]. No PK data is available for critically ill patients, but higher doses of tigecycline could be easily used with very few expected side effects [119]. Dosage regimens for obese, critically ill patients should be no different than regimens for non-obese patients (Table 3).

Lipopeptides

Daptomycin is concentration dependent with time-dependent lipopeptide administered to treat gram-positive infections. The PK/PD index that best predicts efficacy is C_{max}/MIC or AUC_{0-24}/MIC > 600 [120]. Dosing recommendations for patients with normal renal function is 6 mg/kg of TBW/day. If the patient presents renal insufficiency, the interval between doses needs to be increased [121]. However, a recent PK study in critically ill patients receiving 6–8 mg/kg of daptomycin showed that CL was increased and antibiotic exposure decreased in septic patients. Falcone et al. have thus suggested that higher dosage regimens may be needed in these patients, such as 500–750 mg/day of daptomycin [122].

Pai et al. confirmed that TBW was the appropriate dosing weight for morbidly obese subjects in a PK study evaluating a single dose of daptomycin given in 7 normal-weight and 7 morbidly obese, healthy volunteers. PK data showed an increase in the C_{max} and the AUC_{0-24} in the obese group, but these changes were due to the increase in the overall dose administered. Indeed, no difference was observed between obese and non-obese patients when AUC_{0-24} and C_{max} were normalized to TBW. Also, drug CL was similar in both groups [123]. On the other hand, Dvorchik and Damphousse found that obese patients had lower CL of daptomycin than normal-weight individuals with matched renal functions. The conflicting results are probably due to the utilization of the Cockcroft-Gault equation to estimate renal function in this latter study, which probably overestimated renal function in the morbidly obese patients [121]. There is no PK data in the obese, critically ill patient. Currently, no dosage adjustment should be made in this patient population (Table 3).

Conclusions

We have reviewed the existing literature on antibiotic regimens in obese, critically ill patients. Adequate antibiotic regimens are important to prevent excessive serum concentrations and toxicity but also to avoid insufficient serum concentrations and potential therapeutic failure. However, despite the growing number of obese patients, PK studies on antibiotics in this patient population are greatly lacking. Furthermore, there are a number of limitations in the studies already performed. Sample sizes are often small; most of the studies compare the PK data obtained from obese individuals with historical control groups from the literature; and only total antibiotic serum concentrations are measured while the unbound fraction is then calculated. Thus, the dosage recommendations must be considered with caution. Finally, despite that increased VD of drugs has been observed in obese patients, different loading doses in this patient population have not been widely explored. More PK studies in this patient population are clearly warranted. Also, because of the large inter- and intra-individual variability of the drug PKs in the critically ill patient [67], we recommend TDM of all antibiotics administered, whenever possible to optimize drug therapy.

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References

1. World Health Organization. Obesity. Available from http://www.who.int/topics/obesity/en/. [Accessed on 15 November, 2014]
2. Ogden CL, Carroll MD, Kit BK, Flegal KM (2012) Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA 307:483–90
3. Marketing of foods high in salt fat and sugar to children. Copenhagen: WHO Regional Office for Europe; 2013. Available from http://www.euro.who.int/en/health-topics/Life-stages/child-and-adolescent-health/publications/2013/marketing- of-foods-high-in-fat,-salt-and-sugar-to-children-update-20122013. [Accessed on 25 October, 2014]
4. Ng M, Fleming T, Robinson M, et al (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384:766–81
5. Wang YC, McPherson K, Marsh T, et al (2011) Health and economic burden of the projected obesity trends in the USA and UK. Lancet 378:815–25
6. Falagas ME, Kompoti M (2006) Obesity and infection. Lancet Infect Dis 6:438–46
7. Falagas ME, Athanasoulia AP, Peppas G, Karageorgopoulos DE (2009) Effect of Body mass index on the outcome of infections: a systematic review. Obes Rev 10:280–9
8. Choban PS, Heckler R, Burge JC, Flancbaum L (1995) Increased incidence of nosocomial infections in obese surgical patients. Am Surg 6:1001–5
9. Bertakis KD, Azari R (2005) Obesity and the use of health care services. Obes Res 13:372–9
10. Vincent JL, Rello J, Marshall J, et al (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA 302:2323–9
11. Vazquez-Guillamet C, Scolari M, Zilberberg MD, et al (2014) Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med 42:2342–9
12. Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37:840–51

13. Udy AA, Roberts JA, Lipman J (2013) Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 39:2070–82
14. Hites M, Dell'Anna AM, Scolletta S, et al (2014) The challenges of multiple organ dysfunction syndrome and extra-corporeal circuits for drug delivery in critically ill patients. Adv Drug Deliv Rev http://dx.doi.org/10.1016/j.addr.2014.05.007
15. Taccone FS, Laterre PF, Spapen H, et al (2010) Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care 14:R53
16. Taccone FS, Laterre PF, Dugernier T, et al (2010) Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14:R126
17. Beumier M, Roberts JA, Kabtouri H, et al (2013) A new regimen for continuous infusion of vancomycin during continuous renal replacement therapy. J Antimicrob Chemother 68:2859–65
18. Van Zanten ARH, Polderman KH, van Geijlswijk IM, et al (2008) Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. J Crit Care 23:422–30
19. Drusano GL (2004) Antibiotic pharmacodynamics: critical interactions of "bug and drug" Nature Reviews 2:289–300
20. Jackson SJ, Leahy FE, McGowan AA, et al (2004) Delayed gastric emptying in the obese: an assessment using the noninvasive (13)C-octanoic acid breath test. Diab Obes Metab 6:679–88
21. Cockshott WP, Thompson GT, Howlett LJ, Seeley ET (1982) Intramuscular or intralipomatous injections? N Engl J Med 307:356–8
22. Genderson K, Shen G (1966) Total body water in obesity. Am J Clin Nutr 19:77–83
23. Forbes GB, Welle SL (1983) Lean body mass in obesity. Int J Obes 7:99–107
24. Benedek IH, Blouin RA, McNamara PJ (1984) Serum protein binding and the role of increased α1-acid glycoprotein in moderately obese male subjects. Br J Clin Pharmacol 18:941–6
25. Mavrelis PG, Ammon HV, Gleysteen JJ, et al (1983) Hepatic free fatty acids in alcoholic liver disease and morbid obesity. Hepatology 3:226–31
26. Blouin RA, Kolpek JH, Mann HJ (1997) Influence of obesity on drug disposition. Clin Pharm 6:706–14
27. Morita K, Yamaji A (1995) Changes in the serum protein binding of vancomycin in patients with methicillin resistant *Staphylococcus aureus* infection: the role of serum α1-acid glycoprotein levels. Ther Drug Monit 17:107–12
28. Suh B, Craig WA, England AC, Elliott RL (1981) Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis 149:986–97
29. Summers LK, Samra JS, Humphreys SM, et al (1996) Subcutaneous abdominal adipose tissue blood flow: variation within and between subjects and relationship to obesity Clin Sci (Lond) 91:679–83
30. Rossi M, Nannipeiri M, Anselmino M, et al (2012) Subcutaneous adipose tissue blood flow and vasomotion in morbidly obese patients: long term effect of gastric bypass surgery. Clin Hemorheol Microcirc 51:159–67
31. Brill MJE, Houwink API, Schmidt J, et al (2014) Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. J Antimicrob Chemother 69:715–23
32. Hollenstein UM, Brunner M, Schmid R, et al (2001) Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord 25:354–8
33. Joukhader C, Dehghanyar P, Traunmuller F, et al (2005) Increase of microcirculatory blood flow enhances penetration of ciprofloxacin into soft tissue. Antimicrob Agents Chemother 49:4149–53
34. Machado MV, Cortez-Pinto H (2014) Non-alcoholic fatty liver disease: what the clinician needs to know. World J Gastroenterol 20:12956–80
35. Brill MJ, Diepstraten J, van Rongen A, et al (2012) Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 51:277–304
36. Kotlyar M, Carson SW (1999) Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther 37:8–19
37. Abernethy DR, Greenblatt DJ, Divoll M, Shader RI (1983) Enhanced glucoronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med 101:873–80
38. Ebert EC (2006) Hypoxic liver injury. Mayo Clin Proc 81:1232–36
39. Hiramatsu A, Takahashi S, Aikata T, et al (2008) Etiology and outcome of acute liver failure: retrospective analysis of 50 patients treated at a single center. J Gastroenterol Hepatol 23:1216–22
40. Büdingen FV, Gonzalez D, Tucker AN, et al (2014) Relevance of liver failure for anti-infective agents: from pharmacokinetic alterations to dosage adjustments. Ther Adv Infect Dis 2:17–42
41. Barth J, Jäger D, Mundkowski R, et al (2008) Single- and multiple-dose of pharmacokinetics of intravenous moxifloxacin in patients with severe hepatic impairment. J Antimicrob Chemother 62:575–8
42. Montay G, Gaillot J (1990) Pharmacokinetics of fluoroquinolones in hepatic failure. J Antimicrob Chemother 26S:61–7
43. Naora K, Ichikawa N, Hirano H, Iwamoto K (1999) Distribution of ciprofloxacin into the central nervous system in rats with acute renal or hepatic failure. J Pharm Pharmacol 51:609–16
44. Bosma RJ, Krikken JA, Hman van der Heide JJ, et al (2006) Obesity and renal hemodynamics. Contrib Nephrol 151:184–202
45. Udy AA, Roberts JA, Boots RJ, et al (2010) Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49:1–16
46. Claus BO, Hoste EA, Colpaert K, et al (2013) Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 28:695–700
47. Hites M, Taccone FS, Wolff F, et al (2014) Broad-spectrum β-lactams in obese non-critically ill patients. Nutr Diabetes 4:e119
48. Udy AA, Baptista JP, Lim NL, et al (2014) Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 42:520–7
49. Grundy SM (2004) Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 89:2595–600
50. Harris DG, McCrone MP, Koo G, et al (2015) Epidemiology and outcomes of acute kidney injury in critically ill surgical patients. J Crit Care 30:102–6
51. Piccinni P, Cruz DN, Gramaticopolo S, et al (2011) Prospective multicenter study on epidemiology of acute kidney injury in the ICU: a critical care nephrology Italian collaborative effort (NEFROINT). Minerva Anestesiol 77:1072–83
52. Hites M, Taccone FS, Wolff F, et al (2013) Case-control study of drug monitoring of β-lactams in obese critically ill patients. Antimicrob Agents Chemother 57:708–15
53. WHO expert consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363:157–63
54. Spellwin G. BMI for Men increases Health Insurances for Bodybuilders and Athletes. Available from http://bodybuilding.elitefitness.com/bmi-men-body-builder-athletes?s=7938c37dbc8b3fe898914db0aeee5605. [Accessed on October 24, 2014]
55. Green B, Duffull SB (2004) What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 58:119–33

56. Wurtz R, Itokazu G, Rodvold K (1997) Antimicrobial dosing in obese patients. Clin Infect Dis 25:112–8
57. Janson B, Thursky K (2012) Dosing of antibiotics in obesity. Curr Opin Infect Dis 25:634–49
58. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
59. Cirillo M, Anastasio P, De Santo NG (2005) Relationship of gender, age, and body mass index to errors in predicted kidney function. Nephrol Dial Transplant 20:1791–8
60. Verhave JC, Fesler P, Ribstein J, et al (2005) Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis 46:233–41
61. Aggarwal N, Porter AC, Tang IY, et al (2012) Creatinine-based estimations of kidney function are unreliable in obese kidney donors. J Transplant 2012:872–94
62. Levey AS, Bosch JP, Lewis JB, et al (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–70
63. Salazar DR, Corcoran GB (1988) Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 84:1053–60
64. Demirovic JA, Pai AB, Pai MJ (2009) Estimation of creatinine clearance in morbidly obese patients. Am J Health-Syst Pharm 66:642–8
65. Levey AS, Stevens LA, Schmid CH, et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–12
66. Baptista JP, Udy AA, Sousa E, et al (2011) A comparison of estimates of glomerular filtration in critically ill patients. Crit Care 15:R139
67. Roberts JA, Norris R, Paterson DL, Martin JH (2011) Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 73:27–36
68. Taccone FS, Cotton F, Roisin S, et al (2012) Optimal meropenem concentrations to treat multidrug-resistant Pseudomonas aeruginosa septic shock. Antimicrob Agents Chemother 56:2129–31
69. Newman D, Scheetz MH, Adeyemi OA, et al (2007) Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. Ann Pharmacother 41:1734–39
70. Deman H, Verhaegen J, Willems L, Spriet I (2012) Dosing of piperacillin/tazobactam in a morbidly obese patient. J Antimicrob Chemother 67:782–83
71. Roberts JA, Ulldemolins M, Roberts MS, et al (2010) Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 36:332–9
72. Rich BS, Keel R, Ho VP, et al (2012) Cefepime dosing in the morbidly obese patient population. Obes Surg 22:465–71
73. Chen M, Nafziger AN, Drusano, et al (2006) Comparative pharmacokinetics and pharmacodynamic target attainment of Ertapenem in normal-weight, obese, and extremely obese adults. Antimicrob Agents Chemother 50:1222–27
74. Cheatham SC, Fleming MR, Healy DP, et al (2014) Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. J Clin Pharmacol 54:324–30
75. Roberts JA, Lipman J (2013) Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med 41:489–95
76. Sturm A, Allen N, Rafferty KD, et al (2014) Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy 34:28–35
77. Cheatham SC, Fleming MR, Healy DP, et al (2013) Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. Antimicrob agents 41:52–56
78. Zakrison TL, Hille DA, Namias N (2012) Effect of body mass index on treatment of complicated intra-abdominal infections in hospitalized adults: comparison of ertapenem with piperacillin-tazobactam. Surg Infect 13:38–42
79. Buijk SE, Mouton JW, Gyssens IC, et al (2002) Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intensive Care Med 28:936–42
80. Pai MP, Nafziger AN, Bertino Jr SB (2011) Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. Antimicrob. Agents Chemother. 55:4006–11
81. Pai MP, Rodvold KA (2014) Aminoglycoside dosing in patients by kidney function and area under the curve: the Sawchuck-Zaske dosing method revisited in the era of obesity. Diagnostic Microbiology and Infectious Diseases 78:178–87
82. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA (1983) Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol 24:643–7
83. Ross AL, Tharp JL, Hobbs GR, et al (2013) Evaluation of extended interval dosing aminoglycosides in the morbidly obese population. Adv Pharmacol Sci 2013:194389
84. Wysocki M, Delatour F, Faurisson F, et al (2001) Continuous intermittent infusion of vancomycin in severe Staphylococcal infections: Prospective randomized study. Antimicrob Agents Chemother 45:2460–7
85. Cataldo MA, Tacconelli E, Grilli E, et al (2012) Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother 67:17–24
86. Roberts JA, Taccone F, Udy AA, et al (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55:2704–9
87. Blouin RA, Bauer RA, Miller DD, et al (1982) Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother 21:575–80
88. Moffett BS, Kim S, Edwards MS (2011) Vancomycin dosing in obese pediatric patients. Clin Pediatr (Phila) 50:442–6
89. Grace E (2012) Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. Agents Antimicrob Chemoth 67:1305–10
90. Lodise TP, Lomaestro B, Graves J, Drusano GL (2008) Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 52:1330–36
91. Lodise TP, Patel N, Lomaestro BM, et al (2009) Relationship between initial Vancomycin concentration-time profile and nephrotoxicity among hospitalzed patients. CID 49:507–14
92. Van Hal SJ, Paterson DL, Lodise TP (2013) Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemotherap 57:734–44
93. Hanrahan TP, Harlow G, Hutchinson J, et al (2014) Vancomycin-associated nephrotoxicity in the critically ill: a retrospective multivariate regression analysis. Crit Care Med 42:2527–36
94. Conil JM, Georges B, de Lussy A, et al (2008) Ciprofloxacin use in critically ill patients: pharmacokinetic and pharmacodynamic approaches. Intl J Antimcrob Agents 32:505–10
95. Benko R, Matuz M, Doro P, et al (2007) Pharmacokinetics and pharmacodynamics of levofloxacin i critically ill patients with ventilator-associated pneumonia. Intl J Antimicrob Agents 30:162–8
96. Kees MG, Weber S, Kees F, Horbach T (2011) Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients 66:2330–5
97. Allard S, Kinzig M, Boivin G, et al (1993) Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther 54:368–73

98. Utrup TR, Mueller EW, Healy DP, et al (2010) High-dose ciprofloxacin for serious gram-negative infection in an obese, critically ill patient receiving continuous venovenous hemodiafiltration. Ann Pharmacother 44:1660–4
99. Cook AM, Martin C, Adams VR, Morehead RS (2011) Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. Antimicrob Agents Chemother 55:3240–43
100. Luque S, Grau S, Valle M, et al (2011) Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient. J Antimicrob Chemother 66:1653–4
101. Pai MP, Cojutti P, Pea F (2014) Levofloxacin dosing regimen in severely morbidly obese patients (BMI > 40 kg/m^2) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet 53:753–62
102. Mersfelder TL, Smith CL (2005) Linezolid pharmacokinetics in an obese patient. Am J Health Syst Pharm 53:464–7
103. Tsuji Y, Hiraki Y, Matsumoto K, et al (2012) Evaluation of pharmacokinetics in an old obese Japanese patient. Scand J Infect Dis 44:626–29
104. Stein GE, Schooley SL, Peloquin CA, et al (2005) Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. Ann Pharmacother 39:427–32
105. Bhalodi AA, Papasavas PK, Tishler DS, et al (2012) Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother 57:1144–49
106. Meagher AK, Forresr A, Rayner CR, et al (2003) Population pharmacokinetics of linezolid in patients treated in a compassionate-use program. Antimicrob Agents Chemother 47:548–53
107. Boselli E, Breilh D, Rimmele T, et al (2005) Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit Care Med 33:1529–33
108. Buerger C, Plock N, Dehghanyar P, et al (2006) Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically ill patients after multiple dosing using microdialysis. Antimicrob Agents Chemother 50:2455–63
109. Beer R, Engelhardt KW, Pfausler B, et al (2007) Pharmacokinetics of linezolid in cerebral spinal fluid and plasma in neurointensive care patients with Staphylococcal ventriculitis associated with external ventricular drains. Antimicrob Agents Chemother 51:379–82
110. Michalopoulos AS, Falagas ME (2011) Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care 1:30
111. Markou N, Markantonis SL, Dimitrakis E, et al (2008) Colistin serum concentrations after intravenous administration in patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. Clin Therapeutics 30:143–51
112. Plachouras D, Karvanen M, Friberg LE, et al (2009) Population pharmacokinetic analysis of colistin methanesulfonate and colistine after intravenous administration in critically ill patients with infections caused by gram-negative bacteria 53:3430–6
113. Garonzik SM, Li J, Thamlikitkul V, et al (2011) Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing strategies for various categories of patients. Antimicrob Agents Chemother 55:3284–94
114. Mohamed AF, Karaiskos I, Plachouras D, et al (2012) Application of a loading dose of colistin methanesulfate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother 56:4241–9
115. Gauthier TP, Wolowich WR, Reddy A, et al (2012) Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. Antimicrob Agents Chemother 56:2392–6
116. Boisson M, Jacobs M, Grégoire N, et al (2014) Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. Antimicrob Agents Chemother 58:7331–9
117. Xie J, Wang T, Sun J, et al (2014) Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation. Intl J Infect Dis 18:62–7
118. Pai MP (2013) Serum and urine pharmacokinetics of tigecycline in obese class III and normal weight adults. J Antimicrob Chemother 69:190–9
119. De Pascale G, Montini L, Pennisi M, et al (2014) High dose tigecycline in critically ill patients with severe infecions due to multidrug-resistant bacteria. Crit Care 18:R90
120. Safdar N, Andes D, Craig WA (2004) In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 48:63–8
121. Dvorchik B, Damphousse D (2005) The pharmacokinetics of daptomycin in moderately obese, morbidly obese and matched nonobese subjects. J Clin Pharmacol 45:48–56
122. Falcone M, Russo A, Venditti M, et al (2013) Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 57:1568–76
123. Pai MP, Norenberg JP, Anderson T, et al (2007) Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrob Agents Chemother 51:2741–7