REVIEW

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Antibiotic therapy of pneumonia in the obese patient: dosing and delivery

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Purpose of review
Obesity has been shown to be associated with antibiotic underdosing and treatment failure. This article reviews the recent literature on antibiotic dosing in obese patients with pneumonia.

Recent findings
Obesity is associated with several alterations in antibiotic pharmacokinetics and pharmacodynamics, including increases in the antibiotic volume of distribution and clearance. These alterations necessitate changes in the dosing of certain antibiotics. However, data on antibiotic dosing for pneumonia in obese patients are limited and come mainly from observational studies. Additionally, dosing recommendations are often extrapolated from healthy obese volunteers and from the studies of antibiotics given for other indications.

Summary
Recognizing obesity-related pharmacokinetic and pharmacodynamic alterations is important in treating obese patients with pneumonia. Studies that evaluate such alterations and assess the impact of antibiotic dosing and delivery on the clinical outcomes of this patient population are needed.

Keywords
antibiotics, dosing, obesity, pharmacodynamics, pharmacokinetics

INTRODUCTION

Antimicrobial therapy in obese patients for different infections, including pneumonia, represents a clinical challenge because of altered pharmacokinetics and pharmacodynamics. However, this area is understudied and underappreciated. A recent large cohort study of adult patients with septic shock, including patients with pneumonia, showed that the total daily administered doses of commonly used antibiotics did not differ among the different body mass index (BMI) groups [1]. This translated to lower dose per kg in the obese and very obese patients compared with the normal BMI patients even after adjustment for creatinine clearance [1]. Another retrospective study at an emergency department (ED) found that the adherence rates to hospital guidelines for the first dose of cefepime, cefazolin, and ciprofloxacin in patients with weights more than 100 kg and BMI greater than 40 kg/m^2 were only 8.0, 3.0, and 1.2%, respectively [2]. Additionally, obesity has been associated with antibiotic underdosing and treatment failure. A cohort study of mostly outpatients receiving oral antibiotics for different reasons including lower respiratory tract infection found that obesity was a significant predictor of antibiotic treatment failure, defined as any additional antibiotic prescriptions or hospitalizations for infections within 30 days after initial therapy [adjusted odds ratio (OR), 1.26; 95% confidence interval (CI), 1.03–1.52] [3].

In this review, we will highlight the recent studies of commonly used antibiotics in obese patients with community or healthcare-associated pneumonia. We focus on the dosing regimens rather on antibiotic selection, which is beyond the scope of this review. Of note is that most studies have evaluated plasma drug levels as the main endpoint and

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KEY POINTS

- Obesity is associated with several alterations in antibiotic pharmacokinetics and pharmacodynamics.
- Data on antibiotic dosing for pneumonia in obese patients are limited and come mainly from observational studies.
- Obesity should be considered when dosing of β-lactams, vancomycin, or aminoglycosides for the management of pneumonia.

only a few evaluated lung tissue levels. The association of different dosing regimens with clinical endpoints, such as pneumonia recovery, recurrence, and mortality, are seriously understudied.

DEFINITIONS

Table 1 includes the different body weight descriptors, obesity classification, and formulae used to estimate kidney function.

RISK FACTORS FOR DOSING CHANGES IN OBESE PATIENTS

Obesity results in several alterations that affect antibiotic pharmacokinetics and pharmacodynamics. These alterations are summarized in Fig. 1 and discussed below.

Absorption

Studies have shown that delayed gastric emptying may occur in obese people, which may result in lower antibiotic absorption and plasma concentration [4▪]. As a result of higher consumption of fatty meals, absorption might be higher for lipophilic antibiotics [4▪].

Distribution

The volume of distribution (Vd) is a theoretical volume in which a drug amount uniformly distributes to produce the desired plasma concentration. It is calculated by dividing the antibiotic dose by its plasma concentration. A high Vd indicates that the

Table 1. Obesity classification and formulae of body weight descriptors and for kidney function estimation

Weight descriptor formulae		
BMI = weight in kg/(height in m)^2		
IBW for men = 50 kg + 2.3 kg for each inch above 60 inches of height		
IBW for women = 45.5 kg + 2.3 kg for each inch above 60 inches of height		
ABW = IBW + [(C) × (TBW – IBW)]		
C = correction factor, for hydrophilic drugs (0.37–0.58), average 0.4		
Estimated LBW (Kg) for men = (9270 × TBW)/(6680 + 216 × BMI)		
Estimated LBW (Kg) for women = (9270 × TBW)/(8780 + 244 × BMI)		
Obesity classification		
Underweight	BMI <18.5	<80% IBW
Normal weight	BMI = 18.5–24.99	80–125% IBW
Overweight	BMI = 25–29.99	126–190% IBW
Obese class I	BMI = 30–34.99	126–190% IBW
Obese class II	BMI = 35–39.99	126–190% IBW
Obese class III or morbid obesity	BMI = 40–49.9	>190% IBW
Super obesity	BMI >50	>190% IBW
Renal function estimating formulae		
Cockcroft–Gault formula = [(140 – age) × TBW[a]/Scr (mg/dl) × 72] × 0.85 (if woman)		
[a]can be modified by using IBW or ABW instead of actual BW		
The Modification of Diet in Renal Disease equation for estimated GFR (ml/min/1.73 m^2) = 175 × Scr$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if woman)		
Chronic Kidney Disease Epidemiology Collaboration equations for estimated GFR (ml/min/1.73 m^2)		
Women with Scr ≤0.7: GFR = 144 × (Scr/0.7)$^{-0.329}$ × (0.993)^{age}		
Women with Scr >0.7: GFR = 144 × (Scr/0.7)$^{-1.209}$ × (0.993)^{age}		
Men with Scr ≤0.9: GFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)^{age}		
Men with Scr >0.9: GFR = 144 × (Scr/0.9)$^{-1.209}$ × (0.993)^{age}		

ABW, adjusted body weight; BMI, body mass index; GFR, glomerular filtration rate; IBW, ideal body weight; LBW, lean body weight; Scr, serum creatinine (mg/dl); TBW, total body weight.

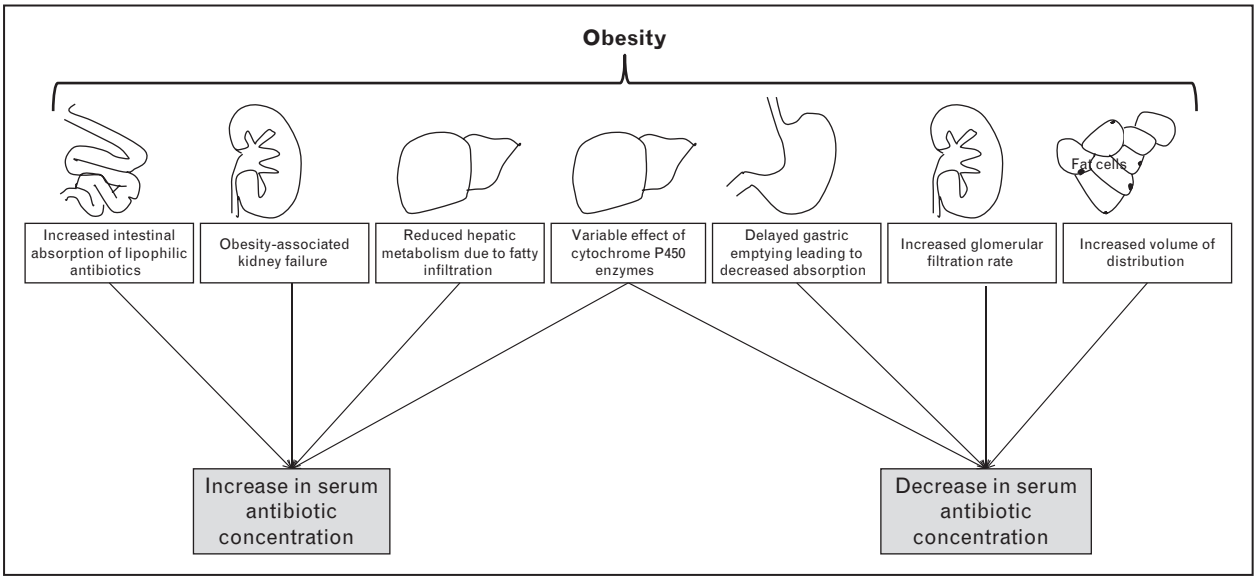

FIGURE 1. Mechanisms by which obesity alters antibiotic pharmacokinetics and pharmacodynamics.

drug extensively distributes to tissues and a low Vd indicates that the drug is concentrated in the plasma [4▪]. Vd is affected by the medication properties including lipophilicity, hydrophilicity, plasma protein binding, and molecular weight [4▪]. Lipophilic medications are generally associated with higher Vd, whereas hydrophilic medications are associated with lower Vd (Fig. 1) [4▪]. Obesity increases Vd, especially for lipophilic antibiotics, because of increased lean body mass and increased adipose tissue which can lead to lower than expected plasma antibiotic concentrations. Of note, Vd may further increase during critical illness, especially for hydrophilic medications because of capillary leak and fluid resuscitation [5]. Taking into consideration the other properties of the antibiotics and the clinical presentation, the total body weight (TBW) is generally recommended for dosing of lipophilic antibiotics and the ideal or adjusted body weight for hydrophilic antibiotics.

Metabolism

In obesity, fatty infiltration of the liver may lead to hepatic dysfunction. Additionally, the levels of certain cytochrome P450 enzymes increase and others decrease or do not change [4▪]. However, the influence of obesity on hepatic antibiotic metabolism is largely unknown.

Renal clearance

Obese individuals have increased antibiotic clearance from the systemic circulation because of increased kidney mass and glomerular filtration. This may become even more relevant during critical illness [6], likely because of the systemic inflammatory response syndrome compounded by fluid resuscitation and vasoactive medications. In a prospective observational study in surgical and medical ICU patients ($n = 128$) receiving antibiotics, augmented renal clearance, defined as at least one creatinine clearance (CL_{cr}) greater than 130 ml/min/1.73 m^2, was present in 51.6% of them and was associated with higher treatment failure (27.3 versus 12.9%; $P = 0.04$) [6]. However, obese patients with chronic hypertensive or diabetic nephropathy may have decreased antibiotic clearance. Antibiotic dosing in obese patients should take into consideration these variations in kidney function. Unfortunately, studies have shown that the equations that estimate kidney function (Table 1) do not provide accurate results in obese patients. A study found that the Chronic Renal Insufficiency Cohort glomerular filtration rate (GFR)-estimating equation was less accurate in obese compared with nonobese patients [7]. Another study found that Cockcroft–Gault, Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration formulae performed poorly in obese potential kidney donors [8]. In the same study, CL_{cr} measurement based on 24-h urine collection performed better, although this finding was based only on data from the 15% of patients who had adequate urine collection [8]. Considering the inaccuracies of CL_{cr} and GFR equations, direct measurement of CL_{cr} in critically ill obese may be needed.

Pharmacodynamic considerations

Figure 2 describes the most important antibiotic pharmacokinetics and pharmacodynamics

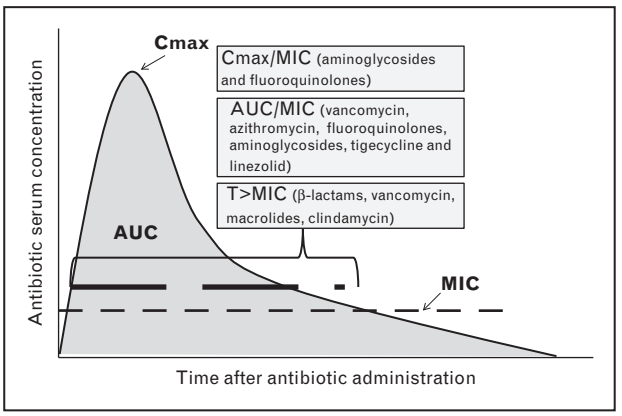

FIGURE 2. Pharmacokinetic and pharmacodynamic parameters. AUC, area under the curve; AUC/MIC, ratio of AUC to MIC (time and concentration-dependent antibiotics); C_{max}, peak antibiotic concentration; C_{max}/MIC, ratio of peak concentration to MIC (concentration-dependent antibiotics); MIC, minimum inhibitory concentration for a pathogen; T > MIC, percentage of time that the antibiotic concentration remains above MIC (time-dependent antibiotics).

parameters. These are the percentage of time that the antibiotic concentration remains above the minimum inhibitory concentration (T > MIC), the ratio of peak concentration to MIC (C_{max}/MIC), and the ratio of the area under the concentration–time curve to MIC (AUC/MIC) [4▪]. T > MIC predicts the efficacy of time-dependent antibiotics (Fig. 2) [4▪]. The ideal concentration is 2–4-fold the MIC of the pathogen [4▪] throughout the dosing interval. T > MIC can be optimized by increasing antibiotic dose or frequency or using continuous or extended infusions [4▪,5]. The C_{max}/MIC predicts the efficacy of concentration-dependent antibiotics (Fig. 2) [4▪]. C_{max} is dependent on the dose and is inversely related to Vd. The AUC_{24h}/MIC predicts the efficacy of antibiotics with mixed properties (Fig. 2) [4▪]. AUC_{24h}/MIC can be optimized by increasing the antibiotic dose. Obesity may decrease T > MIC, C_{max}/MIC, and AUC_{24h}/MIC mainly by affecting antibiotic Vd and clearance.

ANTIBIOTIC DOSING AND DELIVERY IN OBESE PATIENTS

Figure 3 describes the effect of obesity on hydrophilic and lipophilic antibiotics used in pneumonia treatment and the general dosing recommendations. Additionally, Table 2 [4▪,9,10▪–12▪,13–21,22▪,23–25,26▪,27–29] summarizes the specific dosing recommendations for such antibiotics. Here, we review the recent evidence for dosing antibiotics for pneumonia management.

β-Lactams

A study that evaluated critically ill patients (49 obese and 59 nonobese patients; 49% with lung infection) who had received broad-spectrum β-lactams (cefepime, piperacillin and tazobactam, or meropenem) at standard dosing regimens found considerable variability in β-lactam serum concentrations (coefficient of variation of 50–92% for all drugs) in obese and nonobese patients [30]. The standard dosing regimens resulted in insufficient plasma concentrations in 32% of patients and overdosed concentrations in 25% [30]. For meropenem, more obese patients had concentrations that did not reach therapeutic targets than nonobese patients (35 versus 0%; $P = 0.02$), but no differences were observed for cefepime and piperacillin and tazobactam [30]. In the same study, patients on continuous renal replacement therapy were more likely to have supertherapeutic β-lactam serum concentrations and less likely to have insufficient β-lactam serum concentrations [30].

Piperacillin and tazobactam

There is little information regarding penicillin dosing in the obese population with pneumonia. The pharmacokinetic properties of piperacillin and tazobactam have been described in obese patients with infections other than pneumonia. In a 33-year-old morbidly obese patient (BMI = 55 kg/m^2) with a surgical site infection following a transfemoral left leg amputation receiving piperacillin and tazobactam at 4.5 g every 6 h as a 30-min infusion, the percentage free drug T > 4 × MIC and percentage free drug T > MIC were 25 and 60% of the dosing interval, respectively [9]. A study of 14 hospitalized obese patients (weight >120 kg, BMI = 52.3 ± 10.8 kg/m^2) receiving piperacillin and tazobactam 4.5 g every 8 h or 6.75 g every 8 h infused over 4 h found the pharmacokinetics were different compared with nonobese patients [10▪]. For piperacillin, the probability of target attainment for at least 50% of free drug T > MIC was at least 91% for doses of at least 4.5 g every 8 h at MICs of 16 μg/ml or less [10▪]. For tazobactam, the probability of target attainment was 57, 84, and 94% for doses of 4.5, 6.75, and 9.0 g every 8 h, respectively [10▪]. On the basis of the available data, higher doses of piperacillin and tazobactam and longer infusion time of up to 4 h may be required in obese patients.

Cephalosoprins

Analysis of serial serum cefepime concentrations after dosing in 10 morbidly obese patients (BMI

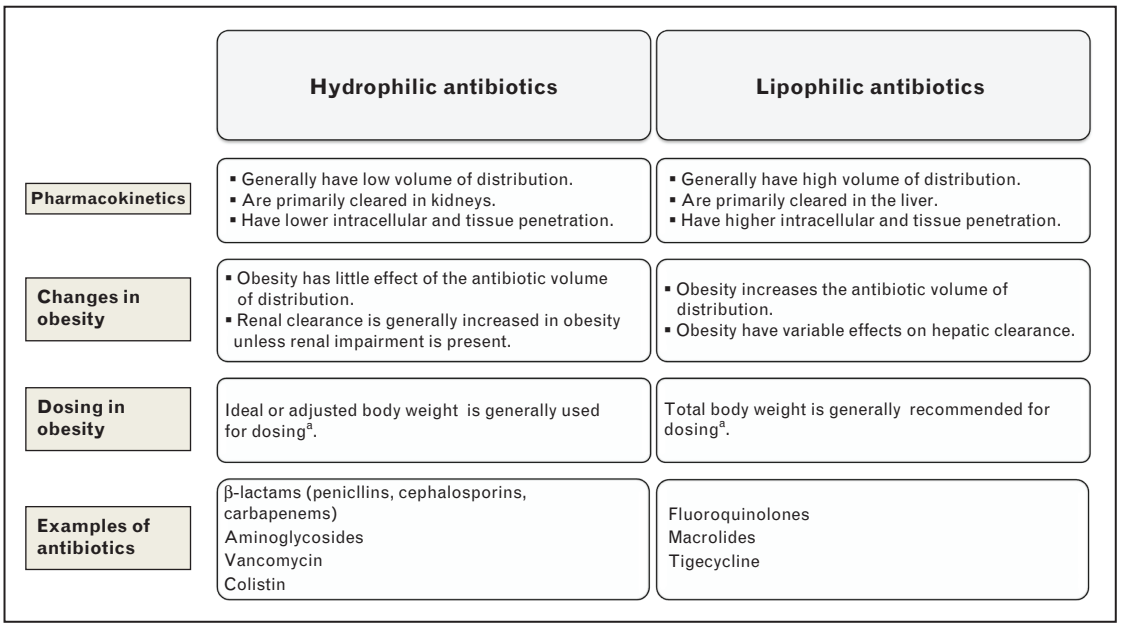

FIGURE 3. Effects of obesity on the pharmacokinetics and pharmacodynamics of hydrophilic and lipophilic antibiotics used in pneumonia treatment and general dosing recommendations. [a]Refer to Table 2 for specific antibiotic recommendation.

$>40\,kg/m^2$; estimated GFR $= 108.4 \pm 34.6$ ml/min) found that an increased dose of 2 g every 8 h was necessary to maintain an adequate free drug T > MIC throughout the dosing interval [11▪]. Therefore, the use of the upper limit of normal doses of cephalosporins is recommended in obese patients.

Carbapenems

In nine ICU patients with BMI of at least $40\,kg/m^2$ who received meropenem (500 mg or 1 g every 6 h, infused over 0.5 h), Monte Carlo simulation was performed for five meropenem dosing regimens (500 mg every 8 h, 1 g every 8 h, 2 g every 8 h, 500 mg every 6 h, and 1 g every 6 h) infused over

Table 2. Dosing recommendations of commonly used antibiotics in obese patients with pneumonia

Antimicrobial class	Dosing recommendations in obese patients with pneumonia	References
Penicillins	Higher doses of piperacillin and tazobactam and longer infusion time of up to 4 h.	[9,10▪]
Cephalosporins	The upper limit of normal doses is recommended.	[11▪]
Carbapenems	The upper limit of normal doses with extended infusions over approximately 3–4 h is recommended.	[12▪,13,14]
Fluoroquinolones	Dose adjustment is probably not warranted for levofloxacin and moxifloxacin. Doses of up to 800 mg every 12 h of ciprofloxacin should be considered in morbidly obese patients.	[4▪,15–17]
Macrolides	Standard doses are recommended. Whether higher doses and longer durations should be used remains uncertain.	[4▪]
Aminoglycosides	The loading dose should be based on adjusted or lean body weight with subsequent dose and interval based on kidney function and drug level.	[18,19]
Vancomycin	The loading dose is 25–30 mg/kg of total body weight in seriously ill patients. Maintenance dose is 15–20 mg/kg of total body weight every 8–12 h, not to exceed 2 g per dose for patients with normal kidney function. Serum trough concentration should be measured prior to the fourth or fifth dose. Target trough concentrations of 15–20 μg/ml are recommended. Doses >1.5 g should be infused over ≥1.5 h.	[20]
Linezolid	Standard linezolid dosing with consideration of continuous infusion is recommended.	[21,22▪]
Colistin	Dosing colistin using ideal body weight is recommended. Loading doses are suggested.	[23,24]
Voriconazole	Dosing based on adjusted or ideal body weight is recommended.	[25,26▪,27]
Oseltamivir	Early standard oseltamivir dosing is recommended with dose increase to 150 mg every 12 h in severe disease and normal kidney function.	[28,29]

0.5 and 3 h [12▪]. The study found that free drug T > MIC for 40% of the dosing interval would be achieved at a probability of at least 90% in four of five regimens infused over 0.5 h and for five of five regimens infused over 3 h [12▪]. Free drug T > MIC for 54% of the dosing interval would be achieved at at least 90% probability in two of five regimens infused over 0.5 h in four of five regimens infused over 3 h [12▪]. In a case report, an obese patient (BMI = 35 kg/m^2) with ventilator-associated pneumonia (VAP) due to *Pseudomonas aeruginosa* (multidrug resistant but meropenem sensitive with MIC = 2 mg/l) was given meropenem (1 g every 8 h) [13]. On days 2 and 5 of therapy, serum meropenem measurements found that meropenem T > 4 × MIC was less than 40% of the dose interval [13]. When meropenem dose was increased to 3 g every 6 h given as a 3-h extended infusion, T > 4 × MIC increased to nearly 50%. The patient's clinical status improved thereafter with resolution of sepsis signs [13]. A study of doripenem in critically ill adult patients with nosocomial pneumonia found that its administration by extended infusion (4 h) negated much of the pharmacokinetic variability caused by different body weights and renal function, and enabled achievement of the concentrations associated with maximal bacterial killing [14]. Hence, the use of the upper limit of normal doses of carbapenems with extended infusions over approximately 3–4 h is recommended in obese patients.

Fluoroquinolones

Data about fluoroquinolones' pharmacokinetics and pharmacodynamics in obese patients are limited. In a 179-kg man, levofloxacin 750 mg every 12 h versus 750 mg daily resulted in an AUC approximately double that found in the nonobese healthy population [15]. In contrast, another study evaluated levofloxacin (750 mg intravenously over 90 min) in 15 obese people (12 hospitalized and 3 ambulatory volunteers), and found that peak concentrations and Vd were similar in the acutely ill obese patients, the ambulatory obese volunteers, and historical normal-weight volunteers [16]. Additionally, levofloxacin clearance was higher (>2×) in the ambulatory obese than the acutely ill obese patients, which resulted in significantly lower AUC [16]. Moxifloxacin was assessed in 12 morbidly obese patients and found that its serum pharmacokinetics were comparable to historical data in normal-weight individuals [17]. In conclusion, optimal dosing of fluoroquinolones in the obese population is difficult to determine, but dosage adjustment is probably not warranted. Older data suggest that ciprofloxacin is affected by obesity and doses up to 800 mg every 12 h should be considered in morbidly obese patients [4▪].

Macrolides

The effect of macrolides against most bacteria is considered to be time dependent with significant postantibiotic effect. Data on macrolide use in obese patients with pneumonia are scarce. For *Helicobacter pylori* treatment, higher doses and longer durations of macrolide therapy have been suggested [4▪]. Whether higher doses and longer durations should be used in obese patients with pneumonia remains uncertain.

Aminoglycosides

Aminoglycoside dosing is based on weight and kidney function, with subsequent dosage modifications guided by therapeutic drug monitoring. Dosing on ideal body weight (IBW) tends to underdose obese patients, whereas dosing on TBW tends to overdose them. Adjusted body weight (ABW) is usually recommended for aminoglycosides dosing (Table 1). One study evaluated ABW for weight-based dosing in 31 morbidly obese patients who received gentamicin or tobramycin 5–7 mg/kg every 24 h [18]. Serum drug concentration was therapeutic in 71%, supratherapeutic in 13%, and subtherapeutic in 16% [18]. The only variable that correlated with supratherapeutic levels was older age ($P = 0.04$) [18]. Another study demonstrated that estimated lean body weight (LBW) (Table 1) was better than TBW and IBW to predict aminoglycoside Vd, and showed an improved prediction of aminoglycoside clearance using equations that estimate GFR rather than CL_{cr} (Table 1) [19]. Even when aminoglycosides achieve therapeutic lung concentrations, they might be inactivated by local conditions in the infected areas of the lung, including local hypoxia, cellular debris, and tissue acidosis, thus decreasing their effectiveness in pneumonia. In conclusion, aminoglycosides should be used in combination regimens for pneumonia treatment. Loading dose should be based on ABW or LBW, with subsequent dose and interval based on estimated GFR and drug level.

Vancomycin

Studies in obese patients demonstrated higher vancomycin clearance in young adult morbidly obese patients that necessitates higher doses to have adequate trough concentration [4▪]. Vancomycin loading below the recommended dose was thought

to contribute to delay in the achievement of therapeutic drug concentrations in one trial for methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia [31]. The 2011 Infectious Diseases Society of America (IDSA) guidelines recommend the following antibiotic regimens for healthcare-associated or community-acquired MRSA pneumonia: intravenous vancomycin (15–20 mg/kg of TBW every 8–12 h, not to exceed 2 g per dose for patients with normal kidney function) or linezolid (600 mg orally/intravenously twice daily), or clindamycin (600 mg orally/intravenously three times daily) for susceptible strains [20]. The guidelines also suggest vancomycin loading dose of 25–30 mg/kg of TBW in seriously ill patients and recommend serum trough concentration measurements prior to the fourth or fifth dose and having vancomycin trough concentrations of 15–20 μg/ml [20]. Individual doses of 1.5 g or greater should be infused over at least 1.5–2 h [20].

Linezolid

Twenty adult obese volunteers (BMI = 30–54.9 kg/m^2) receiving five linezolid doses (600 mg intravenously every 12 h) had AUC exposures similar to those of nonobese patients [21]. In 12 critically ill patients with VAP (median weight = 80 kg), linezolid (loading dose = 600 mg followed by 1200 mg/day by continuous infusion) resulted in a linezolid alveolar diffusion of 100% and concentrations exceeding almost twice the susceptibility breakpoint for *Staphylococcus aureus* (4 mg/l) in both serum and epithelial lining fluid for 100% of the time [22▪]. Hence, it is recommended to use standard linezolid dosing in obese patients with pneumonia with consideration of continuous infusion.

Polymixins

Colistin is a metabolite of the prodrug colistimethate sodium (CMS), which has limited data on its colistin pharmacokinetics behavior [23]. Colistin dosing is based on weight and kidney function. Manufacturers of European colistin products recommend 50 000–75 000 IU/kg/day of CMS in 2–3 divided doses (CMS potency = 12 500 IU per mg). Manufacturers of the U.S. product (Coly-Mycin) recommend 2.5–5 mg/kg colistin base activity daily divided in 2–4 doses (colistin base potency = 30 000 IU per mg) [23]. IBW is the recommended dosing weight in obese patients. In critically ill patients with normal kidney function, including those with pneumonia due to multi-drug resistant pathogens, loading dose of 9 million IU followed by 4.5 million IU every 12 h may be the best dose regimen [23]. However, a recent study found that providing 480 mg of CMS as a loading dose in 10 critically ill patients (for VAP in 8, only 1 patient was obese) was associated with significant reduction in the time to bacterial eradication compared with maintenance therapy alone [24]. Notably, obesity (BMI $\geq$31.5 kg/m^2) has been found to be a risk factor for nephrotoxicity (OR, 3.1; 95% CI, 1.15–8.35) in another study [32]. For serum creatinine levels of 1.3–1.5, 1.6–2.5, or at least 2.6 mg/dl, the recommended dosage of intravenous colistin is 2 million IU (160 mg CMS) every 8, 12, or 24 h, respectively [23]. On the basis of the available studies, using IBW in colistin dosing is recommended, taking into consideration the kidney function. Loading doses may be required.

Antifungal agents

A study compared voriconazole plasma trough concentrations and toxicities in obese (BMI >35 kg/m^2) versus normal-weight patients receiving 4 mg/kg voriconazole every 12 h. The obese group had significantly higher trough concentrations (6.2 versus 3.5 mg/l, $P < 0.0001$) and higher rates of supratherapeutic levels (67 versus 17%, $P < 0.0001$) [25]. Therapeutic voriconazole concentrations (2.0–5.5 mg/l) occurred in 29% of obese patients when dosed on TBW, and 45 and 80% of patients when dosed on IBW and ABW, respectively [25]. A retrospective study in patients with hematologic malignancies and hematopoietic stem cell transplants found that patients with higher BMI had higher random voriconazole concentrations with intravenous administration (6.4 mg/l for BMI $\geq$25 kg/m^2 versus 2.8 mg/l for BMI <25 kg/m^2, $P = 0.04$) [26▪]. This was not noted with the oral formulation [26▪]. In a study of 61 ICU patients and patients with hematological malignancies, multivariate analysis revealed that higher BMI was associated with potentially toxic voriconazole plasma concentrations [27]. Dosing based on ABW or IBW is recommended for voriconazole and similarly for amphotericin B.

Neuraminidase inhibitors

Oseltamivir is used to treat severe influenza pneumonia. In a study of obese and lean mice treated with weight-adjusted dosages of oseltamivir, both groups had reduced lung inflammation and similar rates of epithelial cell regeneration rates and were completely protected from influenza mortality [28]. A study in critically ill patients with pandemic H1N1 influenza found that the Vd of the oseltamivir carboxylate metabolite did not increase with increasing

body weight [29]. Studies on the effectiveness of antiviral therapy in obese patients with severe influenza are lacking. Early standard oseltamivir dosing is recommended in obese patients with the dose increased to 150 mg every 12 h in severe disease and normal kidney function.

NEBULIZED ANTIBIOTICS

Because insufficient antibiotic concentrations in the lungs after intravenous administration may lead to poor outcomes, the use of nebulized antibiotics has been suggested to achieve high lung concentrations. A randomized phase II trial of nebulized ceftazidime (15 mg/kg/3 h) and amikacin (25 mg/kg/day) versus intravenous ceftazidime (90 mg/kg/day, continuous infusion) and amikacin (15 mg/kg/day) found similar outcomes in both groups [33]. However, nebulization was associated with obstruction of the expiratory filter in three patients and cardiac arrest in one [33]. A matched case–control study of adjunctive aerosolized and intravenous colistin versus intravenous colistin alone in 208 ICU patients with VAP caused by multi-drug resistant organisms found that aerosolized and intravenous colistin patients had a higher clinical cure rate (69.2 versus 54.8%, $P = 0.03$), fewer days of mechanical ventilation after VAP onset (8 versus 12 days, $P = 0.001$), but similar all-cause mortality [34]. At present, the available evidence does not support modifying the dose or frequency of nebulized antibiotics in obese patients.

ANTIBIOTIC DOSING AFTER BARIATRIC SURGERY

Limited data exist on antibiotic dosing after bariatric surgery. In one study of intravenous and oral moxifloxacin, Roux-en-Y gastric bypass surgery patients compared with healthy volunteers had higher AUC_{∞} (+51 and +54%, respectively) and C_{max} (+25 and +35%, respectively), likely because of higher enterohepatic recirculation after gastric bypass [35]. In a single-dose pharmacokinetic study, azithromycin concentrations and the AUC_{0-24} in gastric bypass patients were lower by 32% ($P = 0.008$) compared with controls [36]. On the other hand, linezolid bioavailability was not changed by Roux-en-Y gastric bypass surgery in one study [37]. In conclusion, there are limited data on antibiotic dosing after bariatric surgery and no recommendations can be made.

FUTURE DIRECTIONS

Data regarding the dosing of antibiotics in obese patients with pneumonia are limited. With the exception of aminoglycosides and vancomycin, the pharmacokinetics and pharmacodynamics of most other antibiotics have not been extensively investigated in the obese population. The role of antibiotic loading doses and therapeutic drug monitoring for antibiotics other than vancomycin and aminoglycosides need further investigation. The correlation between plasma antibiotic concentrations and lung tissue levels in obese patients is lacking and warrants further study. Further studies on the effect of dosing of antibiotics in obese patients with pneumonia on patient-centered outcomes, including recovery, relapse, and mortality, are needed.

CONCLUSION

Obese patients with pneumonia may be incorrectly dosed when obesity-related pharmacokinetics and pharmacodynamics alterations are not recognized. Recommendations for dosing in the obese patient are antibiotic group specific but are generally based on limited evidence. Further studies on the effect of antibiotic dosing in obese patients with pneumonia on patient-centered outcomes are greatly needed.

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None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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