Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2014, **39**, 584–608 doi: 10.1111/jcpt.12200

Review Article

Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review

A. K. Polso PharmD, J. L. Lassiter PharmD and J. L. Nagel PharmD
Department of Pharmacy, University of Michigan Hospitals and Health Centers, Ann Arbor, MI, USA

Received 31 March 2014, Accepted 7 August 2014

Keywords: **antibiotics, antimicrobials, obesity, pharmacodynamic, pharmacokinetic**

SUMMARY

What is known and objective: **Obesity is a significant burden on the healthcare system in the United States, and determining the appropriate antimicrobial dosing regimen in morbidly obese patients is challenging. Morbidly obese patients have documented differences in pharmacokinetic and pharmacodynamic properties compared to normal-weight patients, which impact antibiotic efficacy and toxicity. The Food and Drug Administration does not recognize obesity as a special population and does not require pharmaceutical companies to perform studies specific to obese patients. However, there are an increasing number of post-approval studies in obese patients, and this manuscript reviews available clinical and pharmacokinetic literature regarding weight-based antimicrobial agents. Additionally, we describe a single-centre approach to optimize dosing in morbidly obese patients.**

Methods: **A comprehensive literature search was performed on 15 weight-based antimicrobials in the setting of obesity: acyclovir, aminoglycosides, amphotericin B, cidofovir, colistimethate, daptomycin, flucytosine, foscarnet, ganciclovir, quinupristin/dalfopristin, trimethoprim/sulfamethoxazole, vancomycin and voriconazole. A weight-based antimicrobial dosing guideline for morbidly obese patients was developed. An analysis of guideline compliance and cost analysis were performed following guideline implementation.**

Results and discussion: **This review describes the pharmacokinetic changes that occur in obese patients, including increased volume of distribution, altered hepatic metabolism, renal excretion and changes in protein binding. The majority of weight-based antimicrobials result in increased serum concentrations in morbidly obese patients compared to normal-weight patients when the calculated dose is based on actual body weight.**

What is new and conclusion: **This review demonstrates different antibiotic pharmacokinetic properties are altered in obese patients that could impact efficacy and toxicity. A single-centre guideline for weight-based antimicrobial dosing in obesity was developed and provides recommendations for using ideal body weight, adjusted body weight or actual body weight when calculating antimicrobial doses. However, more research is needed to better elucidate optimal dosing of weight-based antimicrobials in obesity, with particular focus on efficacy and toxicity.**

Correspondence: J. L. Nagel, Department of Pharmacy, University of Michigan Hospitals and Health System, 1111 E. Catherine Street, Room 300, Ann Arbor, MI 48109, USA. Tel.: +1 734 936 2264; fax: +1 734 615 2314; e-mail: nageljl@umich.edu

WHAT IS KNOWN AND OBJECTIVE

Obesity is a major issue in the United States, with 78 million US adults and 12·5 million children and adolescents classified as obese [body mass index (BMI) greater than or equal to 30].[1] This equates to an obesity rate of 35% and 16·9% in adults and children in the United States, respectively.[1] Physiological changes in obesity can alter immunological pathways and increase the risk of central line infection, post-operative surgical site infections, intensive care unit length of stay and risk for severe pneumonia and influenza.[2–5] Additionally, changes in antimicrobial pharmacokinetic and pharmacodynamic properties are well documented, which impact clinical success and risk of toxicity.[2–5] Despite the unique characteristics of the obese patient population, the Food and Drug Administration does not require pharmaceutical manufacturers to evaluate dosing recommendations in obesity. Calculating a weight-based antibiotic regimen is particularly concerning, as most antimicrobials do not significantly penetrate adipose tissue which results in increased serum concentrations in morbidly obese patients.[2–5] Some studies recommend using ideal body weight (IBW) or adjusted body weight (AdjBW) when calculating an antimicrobial dose in morbidly obese patients to strike a balance between obtaining adequate serum antibiotic concentration to effectively treat an infection while attempting to minimize potential toxicities (Table 1).[2–6] Weight-based antimicrobials in this review include acyclovir, aminoglycosides, amphotericin B, cidofovir, colistimethate, daptomycin, flucytosine, foscarnet, ganciclovir, quinupristin/dalfopristin, trimethoprim/sulfamethoxazole, vancomycin and voriconazole. General dosing recommendations in obesity are provided for each agent reviewed; however, the clinician must balance toxicity with efficacy on a case-by-case basis to avoid treatment failure and promotion of antimicrobial resistance. Evaluation of compliance rates and cost savings are analysed following implementation of weight-based antimicrobial dosing recommendations in morbidly obese patients at the University of Michigan Hospitals and Health System (UMHS).

PHARMACOKINETIC ALTERATIONS IN OBESITY

Differences in proportion of adipose tissue, lean muscle tissue and fluid status can greatly affect pharmacokinetic differences between patients, and absorption, distribution, metabolism and excretion are altered in obese patients (Table 2). Modest changes in oral

Table 1. Equations used to calculate body mass index (BMI), lean body weight (LBW), ideal body weight (IBW) and adjusted body weight (AdjBW)

Measure	Formula
BMI (kg/m^2)	BMI = ABW/(height in metres)^2
IBW kg)	Males: IBW = 50 + 2·3 (height in inches − 60 inches) Females: IBW = 45·5 + 2·3 (height in inches − 60 inches)
LBW (kg)	Males: LBW = [9270 × ABW]/[6680 + (216 × BMI)] Females: LBW = [9270 × ABW]/[8780 + (244 × BMI)]
AdjBW (kg)	AdjBW = IBW + [(ABW − IBW) × correction factor]

ABW, actual body weight.

Table 2. Physiological and pharmacokinetic factors altered in obese patients

Parameter	Changes in obesity
Absorption	Changes in gastric motility can alter oral absorption Changes in body composition • Subcutaneous absorption delayed or incomplete with increased adipose tissue • Intramuscular injections mistakenly given as deep subcutaneous injections
Distribution	Little/no change in volume of distribution expected if • Large molecular size • Highly ionized • Highly protein bound • Poorly crosses biological membranes Increase in volume of distribution expected if • Small molecular size • Minimally ionized • Minimally protein bound • Easily crosses biological membranes
Metabolism	Increased fatty infiltration of liver • Altered blood flow and metabolismChange in activity level of cytochrome P450 enzymes
Elimination	Variable effects on kidney function • Increased glomerular filtration rate in healthy obese patients • Possible kidney dysfunction with comorbid conditions

absorption can occur in obesity secondary to delays in gastric emptying, likely caused by differences in dietary habits compared to non-obese subjects.[6] Drug absorption is also delayed or incomplete following subcutaneous injections in morbid obesity. Intramuscular injections may also inadvertently be given as a deep subcutaneous injection due to increased quantity of adipose tissue.[6]

The volume of distribution (V_d) in obesity can be dramatically different compared to normal-weight patients.[2,4,5] The extent of change of drug distribution is primarily based on its intrinsic characteristics such as molecular size, degree of ionization, extent of lipid solubility, protein binding and ability to cross biological membranes.[7] Obesity does not significantly alter albumin binding of medications but may have alterations in lipoproteins and alpha1-acid glycoprotein although studies are inconclusive.[8,9] Other physiological changes, such as tissue blood flow and changes in cardiac output, can also alter drug distribution, although the significance of these changes is yet to be determined.[6,7]

Physiological changes in the liver and kidneys of obese patients can alter metabolism and excretion.[2,4] The increased presence of fatty infiltration in the liver can alter blood flow and thus drug metabolism.[6,7] Additionally, level of cytochrome P450 pathway activity might be altered in obese patients. One study demonstrated increased activity of CYP2E1 and reduced CYP3A4 in obesity, with trends towards change with other CYP isozymes.[9] Obesity can increase glomerular filtration rate (GFR), but this observation is primarily associated with otherwise healthy patients.[2] Obesity in the presence of other comorbidities, especially hypertension, can increase the risk for chronic renal dysfunction.[2] A study conducted in healthy obese patients utilizing common equations for evaluating creatinine clearance or estimated GFR showed both overestimation and underestimation when compared to measured GFR, which can impact the dose and frequency of antimicrobials.[10] Similarly, obese patients in intensive care units may have larger fluctuations in beta-lactam serum concentrations.[11]

REVIEW OF ANTIMICROBIAL AGENTS

Aminoglycosides

Pharmacokinetics of amikacin, gentamicin and tobramycin in obesity are well documented and described in at least 11 human studies (Table 3). Most studies demonstrate a need for dose adjustments in obesity and recommend use of AdjBW. The recommended correction factor varied slightly among studies, which is likely the result of different patient populations and dosing regimens.[2,12–21] Nine studies recommend AdjBW with adjustments ranging from 0·20 to 0·58 [IBW plus 20–58% difference between actual body weight (ABW) and IBW].[2,12,13,15–18,20,21] Only one study did not find a difference in pharmacokinetics between obese and normal-weight patients.[19] This study examined gentamicin and tobramycin in 27 obese peri-partum women and was underpowered to demonstrate statistical significance.

The available literature evaluating aminoglycoside dosing in obesity often has small sample sizes, includes single-dose pharmacokinetic studies and rarely assesses safety. However, the results largely support the use of AdjBW when dosing aminoglycosides in obesity, often with a weight of IBW plus approximately 40% of the excess body weight. Additionally, obesity recommendations are provided in the tobramycin prescribing information, which recommends use of AdjBW [lean body weight (LBW) plus 40% of the excess body weight] when calculating a dosing regimen.[22]

Colistimethate

Colistimethate studies in obesity are described in three retrospective studies, one prospective study and one case report.[23–27] A prospective study by Garonzik *et al.*[26] examined pharmacokinetics of colistimethate in approximately 100 patients with doses ranging from 75 to 410 mg daily. A linear pharmacokinetic model was

Table 3. Antibiotics

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Aminoglycosides				
Tobramycin pharmacokinetics in morbidly obese patients Blouin (1979)	• Single-dose pharmacokinetics study • Morbidly obese women status post-gastric bypass surgery given a 120 mg tobramycin dose • n = 9	• Mean relative V_d was 0·44 L/kg based on IBW and 0·20 L/kg based on ABW	• Not addressed	• 58% of adipose weight must be taken into account to normalize V_d in obese patients • Authors recommend basing dosing schedule on IBW plus 58% of excess weight
Administration of gentamicin to obese patients Korsager (1980)	• Single-dose pharmacokinetic study • Adult, obese patients with >50% excess weight treated with gentamicin for bacterial infections compared to normal-weight patients • Gentamicin 0·8–1·3 mg/kg (capped at 120 mg) • n = 17	• Uptake of gentamicin in adipose tissue found to be 43·7% of uptake in ABW of normal-weight patients • Average apparent V_d in obese and normal patients was 17·7% and 23·0%, respectively • Serum half-life values in obese and normal-weight groups unchanged	• Three patients were excluded due to baseline abnormal serum creatinine	• Authors recommend using AdjBW to determine proper gentamicin dose • AdjBW = (ABW − IBW) × 43·7% + IBW
Aminoglycoside dosing in obese puerperal women Gibbs (1985)	• Non-randomized, prospective study • Obese puerperal women (ABW 30% larger than desirable weight) treated for endometritis • Dosed with 1·5 mg/kg every 8 h, with one group dosed based on AdjBW and another group dosed on ABW (capped at 150 mg per dose) • n = 27	• Average peak serum concentration of 4·7 and 5·5 μg/mL in adjusted and non-adjusted dosing groups, respectively (non-significant different, P-value not reported)	• No patient showed signs of nephrotoxicity • No serum level exceeded 10 μg/mL	• Doses of gentamicin or tobramycin do not need to be adjusted for excess weight initially, although drug concentration monitoring would be recommended
Amikacin pharmacokinetics in morbidly obese patients Bauer (1980)	• Single-dose kinetics study • Morbidly obese post-operative gastric bypass patients given one dose of 1250 mg IV amikacin • n = 7	• Correction factor of 0·38 normalized V_d in obese patients	• Not addressed	• Peak amikacin serum levels can be predicted best when V_d based on IBW plus correction factor of 38% of fat weight is used

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Influence of weight on aminoglycoside pharmacokinetics in normal-weight and morbidly obese patients Bauer (1983)	• Matched, controlled multiple-dose pharmacokinetic study • Normal-weight and morbidly obese patients with normal renal function and documented gram negative infection • Daily doses divided every 8 h: 540 mg gentamicin, 690 mg tobramycin, 1970 mg amikacin • n = 60	• Half-life unchanged between groups • Gentamicin: V_d of 0·17 and 0·25 L/kg ABW ($P < 0·01$) and clearance of 1·02 and 1·31 mL/min/kg ABW ($P < 0·01$) in morbidly obese and normal-weight groups, respectively • Tobramycin: V_d of 0·19 and 0·26 L/kg ABW ($P < 0·01$) and clearance of 1·11 and 1·43 mL/min/kg ABW ($P < 0·01$) in morbidly obese and normal-weight groups, respectively • Amikacin: V_d of 0·18 and 0·26 L/kg ABW ($P < 0·01$) and clearance of 1·07 and 1·37 mL/min/kg ABW ($P < 0·01$) in morbidly obese and normal-weight groups, respectively • Positive correlation between V_d and ABW ($r = 0·751$, $P < 0·05$)	• Not addressed	• Morbidly obese patients required significantly larger mean doses compared to normal-weight patients to achieve comparable serum concentrations • Absolute V_d and clearance are larger in morbidly obese patients • Authors recommend an initial dose based on IBW + 40% fat weight
Amikacin pharmacokinetics in morbidly obese patients undergoing gastric bypass surgery Blouin (1985)	• First-dose, controlled kinetics study • Normal-weight patients (ABW within 15% of IBW) compared to morbidly obese patients undergoing gastric bypass surgery • Normal-weight patients dosed 7·5 mg/kg × ABW, obese patients given 1200 mg dose • n = 13	• Total body clearance was 83·2 and 131·2 mL/min in the control group and presurgery obese group, respectively (non-significant difference when standardized by body surface area of 1·73 m^2) • V_d of 11·6 and 20·0 L in control and presurgery obese group (significant difference even when corrected for IBW or ABW) • P-values not reported	• Not addressed	• Authors recommend increase in amikacin dose for obese patients

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients Pai (2011)	• Prospective evaluation of aminoglycoside pharmacokinetics • Adult patients across extremes of weight • Initial dosing selected by physician, with modifications made my clinical pharmacy service if C_{min} was >2 mg/mL or C_{max} was <5 mg/mL • n = 2073	• V_d relative to LBW relatively constant across weight strata: 0·47, 0·48 and 0·51 L/kg for tobramycin and 0·48, 0·46 and 0·47 L/kg for gentamicin in normal-weight, overweight and obese patients, respectively (no significant differences) • V_d relative to IBW: 0·35, 0·41 and 0·48 L/kg for tobramycin and 0·35, 0·39 and 0·45 L/kg for gentamicin in normal-weight, overweight and obese patients, respectively ($P \leq 0{\cdot}008$ for obese and overweight compared to normal-weight subjects on tobramycin and compared to obese subjects on gentamicin) • V_d relative to ABW: 0·35, 0·33 and 0·30 L/kg for tobramycin and 0·35, 0·32 and 0·27 L/kg for gentamicin in normal-weight, overweight and obese patients, respectively ($P \leq 0{\cdot}008$ for obese and overweight compared to normal-weight subjects on gentamicin and compared to obese subjects on tobramycin)	• Not addressed	• Aminoglycoside dosing can be simplified across all weight strata with use of LBW

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects Schwartz (1978)	• Single-dose kinetics study • Obese and normal subjects given tobramycin or gentamicin at 1 mg/kg (120 mg dose cap) • Indices adjusted to give normal subjects mean adiposity index of 1·0 • n = 26	• Gentamicin V_d relative to ABW was 185 and 244 mL/kg for obese and normal patients, respectively ($P < 0·05$) • Gentamicin V_d relative to AdjBW was 248 and 244 mL/kg for obese and normal patients, respectively (not significant at 0·05 level) • Gentamicin V_d relative to normalized body weight was 337 and 244 mL/kg for obese and normal patients, respectively ($P < 0·05$) • Tobramycin V_d relative to ABW was 232 and 295 mL/kg for obese and normal patients, respectively ($P < 0·05$) • Tobramycin V_d relative to AdjBW 297 and 295 mL/kg for obese and normal patients, respectively (not significant at 0·05 level) • Tobramycin V_d relative to normalized body weight was 365 and 295 mL/kg for obese and normal patients, respectively ($P < 0·05$)	• Not addressed	• Gentamicin and tobramycin distribute less to adipose tissue than to other tissues • Mean relative V_d in obese subjects approximated that in normal subjects when normalized body mass plus 40% of adipose mass were used as total weight in obese subjects
Effect of obesity on gentamicin pharmacokinetics Sketris (1981)	• Prospective, observational pharmacokinetic study • Obese obstetrics/gynaecology patients receiving treatment for gram negative infections • Goal to determine extent of drug distribution to excess weight in obesity • n = 60	• V_d in control group was 0·19 vs. 0·15 L/kg (relative to ABW) in obese patients ($P < 0·01$) • V_d in control group was 0·19 vs. 0·23 L/kg (relative to IBW) in obese patients ($P < 0·025$)	• Not addressed	• Substantial interpatient variability in measurement of distribution volume • Excess weight contributes less volume per kg than IBW or LBW

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Relationship between pharmacokinetic parameters of gentamicin and patient characteristics and/or clinical data in patients with solid organ tumours Ortega (1999)	• Retrospective review • Examined pharmacokinetics of gentamicin and patient characteristics in solid organ tumour cancer patients • n = 198	• Variable best predicting V_d was dosing weight = IBW + 0·2 × (ABW − IBW) (r^2 = 0·325, P < 0·00001) • Cockroft–Gault formula with ABW was best predictor of aminoglycoside clearance in most patients (r^2 ranged from 0·085 to 0·80)	• Not addressed	• Variable best predicting V_d was adjusted weight, whereas clearance was best predicted using ABW in the Cockroft–Gault equation
A standard weight descriptor for dose adjustment in the obese patient Duffull (2004)	• Retrospective review • Adult patients (16–100 years old, BMI 12–52 kg/m^2) • Equations developed to predict normal weight as sum of lean and fat body mass using normal-sized adult oncology patients; predicted normal weight descriptor assessed • n = 3849	• Females with BMI ≥ 32·5 kg/m^2 or males with BMI ≥ 36·2 kg/m^2 are likely to receive a ≥20% larger dose if ABW used as compared to predicated normal weight	• Not addressed	• Both IBW and LBW were better predictors of gentamicin clearance than ABW
Colistimethate				
Acute renal failure associated with sodium colistimethate treatment Elwood (1966)	• Four case reports • Patient 1: 75-year-old obese female with Proteus urinary tract infection, treated with 150 mg TID (6·3 mg/kg/day) sodium colistimethate • Patient 2: 41-year-old female with Pseudomonas urinary tract infection, treated with 150 mg BID (6·3 mg/kg/day) sodium colistimethate • Patient 3: 74-year-old male with polymicrobial urinary tract infection, treated with 300 mg IM daily (5·3 mg/kg) sodium colistimethate • Patient 4: 68-year-old female presented with acute renal failure after receiving 150 mg BID colistimethate × 3 days for Pseudomonas urinary tract infection 2 weeks earlier	• Patient 1: oliguria after fourth injection, with large increase in serum creatinine, potassium and BUN by day 5 • Patient 2: proteinuria, increased serum creatinine, potassium and BUN by day 12 resulting in discontinuation of drug • Patient 3: BUN increase 4 days after initiation; developed complete heart block with elevated potassium; colistimethate was discontinued • Patient 4: anuric by day 5 of colistimethate therapy	• Patient 1: developed acute kidney injury and died after initiation of haemodialysis • Patient 2: died suddenly 6 days after drug discontinued; patient diagnosed with acute tubular necrosis and benign nephrosclerosis • Patient 3: uraemic and died during haemodialysis 8 days after colistimethate was started; patient was diagnosed subacute and chronic pyelonephritis • Patient 4: started peritoneal dialysis for 2 days, with recovery of renal function and discontinuation of dialysis	• Dose range of 5–6·3 mg/kg/day • Pretreatment BUN normal in 3 patients • Dosage should be based on renal clearance of drug, therefore on estimate of glomerular filtration rate • BMI and weights of patients not reported

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicentre study provide dosing suggestions for various categories of patients Garonzik (2011)	• Open-label population pharmacokinetic study • Adults treated with colistin for blood or pneumonia infection due to multidrug-resistant gram negative bacilli • Colistin dosed every 8–24 h based on physician recommendations • n = 105	• Developed model for dosing suggestions: loading dose based on weight; maintenance based on goal steady-state concentration and creatinine clearance • Doses ranged 75–410 mg/day, lower doses for patients with lower creatinine clearance • Body size and creatinine clearance found to be important covariates	• All but 2 patients not on renal replacement had doses of <300 mg/day, and 48% had a rise in serum creatinine of >50%	• Loading dose should use the lower of ABW or IBW • Maintenance dosing should be based on creatinine clearance and target colistin concentrations
Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system Pogue (2011)	• Retrospective cohort study • Patients that received IV colistin for ≥48 h • n = 126	• Nephrotoxicity occurred in 43% of patients, and these patients received higher doses than those who did not develop nephrotoxicity (5·3 mg/kg/day IBW vs. 3·95 mg/kg/day IBW, $P < 0{\cdot}001$) • Statistically significant trend between increasing dosage of colistin and frequency of developing nephrotoxicity ($P < 0{\cdot}001$ for creatinine clearance >50 and creatinine clearance 30–49; $P = 0{\cdot}01$ for creatinine clearance <30 mL/min)	• Per cent of patients with nephrotoxicity risk, injury and failure were 13%, 17% and 13%, respectively • No patients had long-term kidney failure or required haemodialysis	• Toxicity was ≥30% in patients dosed 3–4 mg/kg/day of IBW and 69% when dosed ≥5 mg/kg/day of IBW • It may be challenging to achieve therapeutic levels of colistin without causing significant nephrotoxicity
Colistin dosing and nephrotoxicity in a large community teaching hospital Deryke (2010)	• Retrospective cohort study • Adult patients treated with IV colistimethate sodium for ≥48 h • Dosing regimen determined by creatinine clearance: 5 mg/kg/day if creatinine clearance >80 mL/min; 2·5–3·8 mg/kg/day if creatinine clearance 30–80 mL/min • n = 30	• Average dose using ABW and IBW was 3·9 and 5·1 mg/kg/day, respectively • 47% of patients received an excessive dose, with 71% having been dosed with ABW in an obese patient • 33% of patients developed nephrotoxicity, with renal impairment developing within first 5 days	• 3, 5 and 2 patients were categorized with nephrotoxicity injury, failure and end-stage kidney disease, respectively • Obese patients who received excessive doses based on ABW were 13·2 times more likely to develop nephrotoxicity than those who received normal or low-normal doses	• There appears to be a relationship between developing nephrotoxicity and excessive drug dosing • Excessive dosing was usually due to ABW dosing vs. IBW dosing • BMI was not reported

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients Gauthier (2012)	• Retrospective case-controlled study • Overweight and obese adults (BMI ≥ 25 kg/m^2) who received colistin for ≥72 h • Dosing regimen based on recommendations in package insert with adjustments for renal dysfunction • n = 42	• 48% of patients developed nephrotoxicity in a median of 5 days • BMI ≥ 31·5 kg/m^2, age, diabetes and length of stay prior to getting drug were independent risk predictors of nephrotoxicity	• The per cent of patients categorized with nephrotoxicity risk, injury and failure were 15%, 5% and 80%, respectively	• Nearly 50% rate of nephrotoxicity observed in overweight and obese adults • Excessive dosing due to use of ABW may result in increased risk for nephrotoxicity and more severe kidney injury, whereas under-dosing may increase the chance of treatment failure • Dosing weight not linearly associated with an increased rate of nephrotoxicity, but a BMI ≥ 31·5 kg/m^2 was associated
Daptomycin				
Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin Pai (2007)	• Single-dose pharmacokinetics study • Adult (18–50 years old), morbidly obese (BMI ≥ 40 kg/m^2) matched with normal (BMI 18–25 kg/m^2) female patients • Daptomycin dosed at 4 mg/kg of ABW • n = 14	• C_{max} of 67·3 and 42·3 mg/L (P = 0·029) and $AUC_{0–24}$ of 494 and 307 mg h/L (P = 0·002) in the morbidly obese and normal-weight patients, respectively • The relationship of V_d and total body clearance to weight was best predicted by ABW and BMI	• No serious adverse events reported	• Dosing based on ABW resulted in increased plasma C_{max} and $AUC_{0–24}$ values in morbidly obese subjects • Increases were not due to differences in V_d or clearance

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched non-obese patients Dvorchik (2005)	• Open-label, single-dose, parallel-group study of pharmacokinetics • Morbidly obese (BMI ≥ 40 kg/m^2), moderately obese (BMI 25–39·9 kg/m^2) and non-obese (BMI 18·5–24·9 kg/m^2) patients matched by age, sex and renal function • Daptomycin dosed at 4 mg/kg of ABW • n = 25	• C_{max} of 67·0 and 53·2 μg/mL (P = 0·030) and $AUC_{0-\infty}$ of 548 and 419 μg h/mL (P = 0·004) in moderately obese and non-obese patients, respectively • C_{max} of 58 and 46 μg/mL (P = 0·030) and $AUC_{0-\infty}$ of 421 and 322 μg·h/mL (P = 0·012) in moderately obese and non-obese patients, respectively • Absolute V_d of 11·3 and 7·4 (P < 0·001) in morbidly obese and non-obese subjects, respectively • Weight-normalized (ABW) CL of 7·8 and 10·2 mL/h/kg (P = 0·045) in morbidly obese and non-obese subjects, respectively	• One of seven morbidly obese patients' adverse events determined to be unrelated to daptomycin treatment • Six moderately obese subjects and 12 controls did not experience any adverse events	• Dosing based on ABW resulted in increased plasma C_{max}, AUC_{0-24}, and V_d values in morbidly obese subjects relative to normal-weight subjects • Weight-normalized pharmacokinetics indicate that these differences are not just a result of increased dosing in obese patients • Increased drug exposure does not pose a safety issue
Daptomycin exposure and the probability of elevations in CPK level: data from a randomized trial of patients with bacteremia and endocarditis Bhavnani (2010)	• Subset analysis of phase 3 trial • Patients with *Staphylococcus aureus* bacteremia given daptomycin dosed at 6 mg/kg every day for 10–42 days • n = 108	• Elevated CPK observed in 5·56% of patients, independent of C_{max} • C_{min} ≥ 24·3 mg/L, was significantly associated with elevations in CPK (P = 0·002) • Statistically significant association with obesity (weight ≥ 111 kg) and CPK elevations (P = 0·001)	• Discontinued in 3 patients with musculoskeletal effects • CPK levels returned to normal during treatment or within the post-treatment follow-up period for six patients with elevated CPK	• Daptomycin C_{min} ≥ 24·3 mg/L is associated with an increase in CPK • Obese patients (ABW ≥ 111 kg) were significantly associated with an increase in CPK

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever Bubalo (2009)	• Single-dose pharmacokinetic study • Pharmacokinetics of daptomycin determined in oncology patients (BMI 18·8–45·9 kg/m^2) with neutropenic fever • Daptomycin dosed at 6 mg/kg × ABW every 24 h • n = 29	• Clearance of 18·9, 14·6, 11·9 and 4·3 mL/h/kg in normal-weight, overweight, obese and morbidly obese subjects • Drug concentrations >MIC of 0·12–0·25 μg/mL for 50–100% of the dosing interval • Drug concentrations >MIC of 0·5 for 50–100% of dosing interval in 90% of patients • All patients achieved pharmacodynamic target ratio of C_{max}/MIC and AUC/MIC ratio for *Staphylococcus pneumoniae* and majority for *S. aureus*	• All patients with elevated CPK levels were asymptomatic • No patients experienced myopathy or had daptomycin discontinued due to CPK elevations • One patient experienced rash and one had mental status change	• Daptomycin dosed at 6 mg/kg is effective and well tolerated
Therapeutic drug monitoring-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient Pea (2011)	• Case report • 63-year-old male, BMI 81·6 kg/m^2 with severe cellulitis • Therapeutic drug monitoring	• Estimated V_d used for dose • Dose progressively varied from 1200 mg every 48 h to every 36 h	• Serum CPK increased from baseline of 657 to a peak of 2241 units/L on day 3; normalized on day 7	• Dosed based on estimated V_d, which is lower in obese patients. This supports dosing based on an AdjBW
Daptomycin dosing based on IBW vs. ABW: comparison of clinical outcomes Ng (2014)	• Retrospective cohort study • Compared clinical and microbiological outcomes between ABW and IBW dosing • 40% of ABW and 52% of IBW patients had BMI >30 kg/m^2 • n = 107	• No difference in clinical success (88·9% ABW, 89·1% IBW), even after adjusting for several factors	• No difference in number of adverse events between groups • Over 33% of patients lacked any CPK documentation during therapy	• Study suggests IBW provides similar outcomes to ABW for patients with various infections and organisms • No obese subjects included

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicentre investigation in the south-eastern United States Bookstaver (2013)	• Multicentre retrospective cohort study • • Hospitalized adult obese patients (BMI ≥ 30 kg/m^2) who received daptomycin dose on ABW for any indication for ≥7 days • n = 126	• Clinical effectiveness documented in 71% of patients • Average daptomycin dose of 6·49, 6·51 and 5·83 mg/kg in class I, class II and class III obese patients (P = 0·007)	• CPK elevations >1000 units/L in 8·4% of patients, and elevations >500 units/L in 13·7% of patients • Myalgias reported in 3·2% of patients • Discontinuation of therapy due to adverse drug events occurred in 6·3% of patients • 1 patient developed rhabdomyolysis	• Elevations in CPK are increased in high-risk obese patients, but discontinuation rates remained low
Quinupristin/Dalfopristin				
Open, comparative study of the safety of a single dose of quinupristin/dalfopristin (Q/D, RP 59500) in obese and in non-obese male subjects Lefebvre (1997)	• Single-dose pharmacokinetic study • 7·5 mg/kg × ABW	• 25% increase in C_{max} and AUC in obese patients	• Not addressed	• LBW correlated better with observed concentrations. However, authors recommended use of ABW
Sulfamethoxazole/Trimethoprim				
Surgically affected sulfisoxazole pharmacokinetics in the morbidly obese Garrett (1981)	• Morbidly obese patients after gastric bypass surgery	• V_d unchanged after up to 44% of body weight lost	• Not addressed	• Recommend use of IBW or AdjBW
Vancomycin				
Vancomycin dosing in morbidly obese patients Bauer (1998)	• Retrospective matched study • Vancomycin pharmacokinetics compared between morbidly obese (ABW >90% greater than IBW) and normal-weight adult patients • n = 48	• Good correlation between ABW and clearance (r = 0·948, P < 0·0001) • V_d 0·32 and 0·68 L/kg ABW in obese and non-obese, respectively • Half-life of 3·3 and 7·2 h in obese and non-obese patients, respectively	• Not addressed	• ABW should be used to dose vancomycin in morbidly obese patients with normal renal function • Shortened half-life in obesity may require more frequent dosing

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Vancomycin pharmacokinetics in normal and morbidly obese subjects Blouin (1982)	• Uncontrolled, single-dose pharmacokinetic study • Normal-weight patients pharmacokinetics compared to morbidly obese patients status pose gastric bypass after one dose of vancomycin • n = 10	• Strong positive correlation between ABW and V_d (correlation coefficient 0·943, $P < 0·005$) and total body clearance (correlation coefficient 0·981, $P < 0·001$) • No significant difference in mg/kg daily dose required to reach 15 μg/mL serum concentrations • Terminal half-life of 4·8 and 3·2 h in normal controls vs. morbidly obese patients, respectively	• Not addressed	• ABW should be used for dosing of vancomycin
Vancomycin pharmacokinetics in a patient population: effect of age, gender and body weight Ducharme (1994)	• Retrospective review • Steady-state peak and trough vancomycin data were used to compare pharmacokinetics of vancomycin, including obese patients with ABW >130% IBW • n = 704	• Relative V_d (adjusted for IBW) was 0·7 and 0·63 L/kg in normal-weight females and males, respectively, and 1·17 and 0·90 L/kg in obese females and males, respectively	• Not addressed	• Authors recommend adjusted doses for obesity, age and gender using regression equations
Determining vancomycin clearance in an overweight and obese population Leong (2011)	• Retrospective study • Comparison of two methods for calculating vancomycin clearance to determine best body weight measure to use when dosing in overweight or obese patients • n = 48	• AdjBW was superior in predicting vancomycin clearance and resulting serum concentrations • Only trough levels available	• Not addressed	• AdjBW is superior to ABW when estimating vancomycin clearance in overweight and obese patients
Therapeutic drug monitoring of vancomycin in a morbidly obese patient Penzak (1998)	• Case report and retrospective evaluation of four vancomycin nomograms • 52-year-old, morbidly obese man (307 kg) with MRSA foot ulcers	• ABW was more accurate than IBW in selecting vancomycin dose in all methods except for one nomogram	• No renal insufficiency developed • Patient required below knee amputation	• Regardless of whether using individualized or nomogram vancomycin dosing, ABW and not IBW should be used for empiric dosing

(continued)

Table 3 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Performance of a vancomycin dosage regimen developed for obese patients Reynolds (2012)	• Retrospective review • Comparison of original and revised dosing protocol for obese patients (ABW > 140% IBW) for attainment of target serum trough concentrations and occurrence of nephrotoxicity • Original protocol dosing with ABW was 15 mg/kg every 8–12 h, whereas the revised protocol was 10 mg/kg every 12 h or 15 mg/kg every 24 h • n = 158	• Mean maintenance dose of 34 mg/kg/day with original protocol and 19 mg/kg/day in revised protocol ($P < 0{\cdot}001$) • Revised protocol resulted in increased frequency of target troughs, below-target troughs and decreased frequency of above-target troughs	• Nephrotoxicity occurred in two patients in each study group	• Compared to original dosing protocol, revised protocol with lower total daily doses improved target trough concentrations with minimal nephrotoxicity utilizing ABW
Effect of obesity on vancomycin pharmacokinetic parameters as determined using a Bayesian forecasting technique Vance-Bryan (1993)	• Retrospective review • Fit vancomycin concentration in serum vs. time for each course of therapy with two-compartment Bayesian forecasting programmes • Patients stratified into 9 groups based on body weight • n = 230	• ABW was a significant predictor for V_d and clearance • Per cent over LBW was a significant predictor for V_d and terminal disposition half-life ($P < 0{\cdot}05$)	• Not addressed	• Multiple regression models for pharmacokinetic parameters developed and showed ABW to be superior to LBW for calculating initial dose requirements

V_d, volume of distribution; IBW, ideal body weight; ABW, actual body weight; AdjBW, adjusted body weight; LBW, lean body weight; BMI, body mass index; CPK, creatine phosphokinase.

developed using serum colistin methanesulfonate concentrations and suggested only the loading dose should be weight based. Nearly half of the patients had an increase in serum creatinine of over 50% from baseline, although the impact of weight was not examined on this safety measure.[25]

Pogue *et al.*[23] assessed the incidence of and risk factors for colistimethate-associated nephrotoxicity in a large academic health system in 126 patients. Nephrotoxicity developed in 43% of patients and was associated with a higher mg/kg/day dose of colistimethate (relative to IBW). A statistically significant trend also existed between increasing overall dose and frequency of nephrotoxicity. These results weaken the argument to utilize ABW in dosing. A similar retrospective cohort study by Deryke *et al.*[24] in 30 patients found excessive colistimethate dosing was associated with higher rates of nephrotoxicity (80% vs. 30%, $P = 0{\cdot}019$).

Gauthier *et al.*[25] examined colistimethate in 42 overweight and obese individuals through a retrospective case-controlled study using doses based on prescribing information recommendations. Nearly half of the patients developed nephrotoxicity within a median of 5 days. A BMI of >31 kg/m^2, age, diabetes and length of stay prior to colistimethate initiation were all independent risk factors for nephrotoxicity.

In summary, there are limited data comparing pharmacokinetics of colistimethate in obese vs. normal-weight patients. However, multiple studies demonstrate significant risk of nephrotoxicity with colistimethate in obese patients, and dosing based on IBW or AdjBW may be prudent, with infection severity driving the decision on a case-by-case basis.

Daptomycin

Daptomycin use in obese patients is assessed in six separate human trials and one case report. The drug is a large molecule (1620 Da), highly protein bound (90–95%), and has a fairly small V_d (0·1 L/kg) in healthy volunteers.[28] The prescribing information reports the plasma clearance of daptomycin as 15–23% lower in obese patients based on data from 12 obese or extremely obese patients, which is attributed to decreased renal function as opposed to obesity itself.

Pai *et al.*[29] performed a 4 mg/kg (based on ABW) single-dose pharmacokinetic study in 14 adult female morbidly obese and non-obese patients. The morbidly obese group yielded a 60% increase in C_{max} (67·3 vs. 42·3 mg/L, $P = 0{\cdot}029$) and 60% increase in AUC (494 vs. 307 mg h/L, $P = 0{\cdot}002$) compared to the non-obese group. The relationship of V_d and total clearance with weight was best predicted by ABW ($r^2 = 0{\cdot}66$ and 0·3, respectively) and BMI ($r^2 = 0{\cdot}52$ and 0·24, respectively) when evaluated with linear regression.

Dvorchik *et al.*[30] also performed a single-dose pharmacokinetic evaluation of daptomycin in 25 obese and non-obese patients receiving 4 mg/kg based on ABW. C_{max} and $AUC_{0-\infty}$ increased by 25% and 30%, respectively, in morbidly obese compared to non-obese patients [average C_{max} of 67 vs. 53 μg/mL ($P = 0{\cdot}030$), average $AUC_{0-\infty}$ of 548 vs. 419 μg h/mL ($P = 0{\cdot}004$)]. Absolute V_d increased 55% in morbidly obese relative to non-obese patients.

Bubalo *et al.*[31] examined the pharmacokinetics of daptomycin in 29 oncology patients with neutropenic fever. BMI ranged from 19 to 46 kg/m^2, and daptomycin was dosed at 6 mg/kg ABW. Average daptomycin clearance decreased as BMI increased: 18·93 ± 7·24 mL/h/kg in normal-weight subjects, 14·65 ± 3·08 mL/h/kg in overweight subjects, 11·86 ± 5·16 mL/h/kg in obese subjects and 11·41 ± 4·29 mL/h/kg in morbidly obese subjects. This corresponds to an approximate 60% reduction in total body clearance in obese or morbidly obese patients relative to healthy subjects. A *post hoc* analysis showed a significant difference in clearance between normal-weight and obese subjects ($P = 0{\cdot}015$). No other pharmacokinetic parameters differed significantly by BMI. No patients experienced myopathy or required daptomycin to be discontinued due to elevated creatine phosphokinase (CPK) levels. The authors conclude a 6 mg/kg ABW dose every 24 h was both effective and well tolerated in adult oncology patients.

A case report was also published describing a 63-year-old severely obese male (BMI 81·6 kg/m^2) treated with daptomycin, with dosing dictated by therapeutic drug monitoring.[32] The V_d was anticipated to be approximately 0·09 L/kg based on previous literature in obese patients, but the patient's V_d was 0·08 L/kg, with a C_{max} of 57·48 mg/L after a 1200 mg dose (4·8 mg/kg ABW). CPK increased more than three times the baseline value by day 3 but normalized by day 7. In this case, the use of an adjusted dose resulted in reaching pharmacokinetic goals in an obese patient.

Two studies have demonstrated an increased risk of daptomycin myotoxicity in obese patients.[33,34] A *post hoc* analysis following a phase 3 trial evaluating daptomycin vs. vancomycin in patients with *Staphylococcus aureus* bacteremia was performed by Bhavnani *et al.*,[33] and they examined the incidence and risk factors for adverse events (i.e. elevations in CPK) in 108 patients receiving 6 mg/kg ABW every 24 h. They found CPK elevations in approximately 6% of patients, and risk factors for toxicity were obesity (ABW >110 kg) and daptomycin trough concentration >24·3 mg/L. A multicentre retrospective cohort study by Bookstaver *et al.*[34] included 126 obese patients dosed by ABW for any indication and found CPK elevations of more than 1000 units/L in 8·4% of patients and elevations of more than 500 units/L in nearly 14% of patients. Discontinuation of therapy due to adverse effects of daptomycin occurred in 6·3% of patients, and the authors concluded there were increased CPK elevations in obesity with overall low rates of drug discontinuation.

Finally, Ng *et al.*[35] examined clinical efficacy of daptomycin dosing based on IBW vs. ABW, following an institutional guideline recommending daptomycin dosing based on IBW. They examined 107 patients treated with daptomycin 4–6 mg/kg with *Enterococcus* or *Staphylococcus* infection, with the primary outcome of clinical success (resolution of signs and symptoms of infection and/or no additional gram positive coverage from other antibiotics), or clinical improvement. No statistically significant differences were found between overall clinical and microbiological cure. No significant differences were seen in the number of adverse events in either dosing group; however, CPK levels were only available in 33% of the patients. Nonetheless, prescribing bias was likely present towards less severe infections within the IBW group, as more patients were treated for urinary tract infections.

In summary, there are prospective pharmacokinetic studies recommending the use of ABW, a retrospective study advocating the use of IBW, and a case report that promotes the use of AdjBW when dosing daptomycin in obese patients. Therefore, daptomycin dosing in obese patients based on IBW or AdjBW appears to have similar pharmacokinetics as normal-weight patients, similar efficacy, lower cost and lower risk of adverse effects. Although the rate of CPK elevation is relatively low, utilizing ABW in obese patients is a risk factor for toxicity. More studies are needed that focus on clinical efficacy and toxicity, and dosing should be

determined in the context of infection severity and include close monitoring.

Quinupristin/dalfopristin

Quinupristin/dalfopristin pharmacokinetics in obesity have been examined in one single-dose pharmacokinetics study. In normal healthy patients, the V_d for quinupristin is 0·45 L/kg and for dalfopristin is 0·24 L/kg.[36] Quinupristin has a molecular weight of 1022 Da while dalfopristin is 690 Da, and the per cent protein bound is higher for quinupristin than dalfopristin, although the general percentage is not reported in the package insert. Both compounds are primarily excreted in the faeces, likely through excretion in the bile. Despite the lack of data in obese patients, the prescribing information notes an increase in both C_{max} and AUC by 30–40% in patients with a BMI ≥30 kg/m^2, although no dose adjustments are suggested. A small study performed in 1997 found that both C_{max} and AUC increased by 25% in obese patients (BMI > 30 kg/m^2) relative to non-obese patients after 7·5 mg/kg of quinupristin/dalfopristin based on ABW.[37] Decisions regarding the appropriate weight to use for dosing should be made on a case-by-case basis while balancing risk vs. benefit and taking into consideration disease severity.

Sulfamethoxazole/trimethoprim

Sulfamethoxazole/trimethoprim pharmacokinetics in obesity have not been examined in human studies; however, one small human study in a related sulphonamide antibiotic, sulfisoxazole, has been performed. Sulfamethoxazole/trimethoprim is lipophilic, highly protein bound (70% for sulfamethoxazole, 44% for trimethoprim) and excreted primarily through the kidneys.[38] Both components are similarly small at 253 and 290 Da for sulfamethoxazole and trimethoprim, respectively.

A small study performed by Garrett *et al.*[39] examined pharmacokinetic properties of 1 g of IV sulfisoxazole, another sulphonamide antibiotic with similar pharmacokinetic properties to sulfamethoxazole, in four morbidly obese patients after jejunal–ileal bypass surgery. Pharmacokinetic parameters were collected after a single dose prescribed at 1 week presurgery and 1 week, 6 weeks, 6 months, and 12 months after surgery, and renal function remained stable throughout the study. Although up to 44% of body weight was lost after the first year, V_d did not change, suggesting an obese individual may require a dose similar to a normal-sized individual – for weight-based dosing, this would involve using an AdjBW. Safety was not assessed.

Ultimately, without clinical data to support a specific dosing strategy, decisions regarding the appropriate weight to use for dosing should be made on a case-by-case basis. Monitoring for signs of clinical improvement and drug toxicity is crucial.

Vancomycin

Vancomycin pharmacokinetics in obesity are extensively examined in the literature. The drug is primarily eliminated via the kidneys, 55% bound to serum proteins, and V_d ranges from 0·3 to 0·43 L/kg in normal-weight patients.[40] The prescribing information for vancomycin does not address its use in obese patients.

A retrospective matched study by Bauer *et al.*[41] examined vancomycin pharmacokinetics in 48 morbidly obese and non-obese patients. When normalized by ABW, clearance and V_d did not differ between groups, but a reduced half-life was observed in the obese group. A study by Vance-Bryan *et al.*[42] assessed vancomycin concentrations in 230 patients stratified by body weight. ABW was a significant predictor for both V_d, and multiple regression models showed ABW was superior to LBW when determining initial dosing requirements. Safety was not assessed in any of these retrospective studies. Finally, a case report by Penzak *et al.*[43] detailing a morbidly obese male with methicillin-resistant *S. aureus* foot ulcers treated with vancomycin showed ABW as opposed to IBW was more accurate in predicting the best dose for the patient in three of four dosing nomograms.

Blouin *et al.* published a prospective trial examining vancomycin dosing in obesity. In an uncontrolled, multiple-dose pharmacokinetic study, four non-obese patients were compared to six morbidly obese patients who received a single dose of vancomycin after gastric bypass.[44] Authors observed a strong positive correlation between ABW and both V_d and clearance of vancomycin (correlation coefficient of 0·94 and 0·98, respectively). No significant difference in mg/kg daily dose required to reach the goal drug serum concentration of 15 μg/mL was noted between groups. These data support the use of ABW when dosing vancomycin in obese patients.

Another large retrospective study including 700 patients by Ducharme *et al.*[45] looked at the pharmacokinetics of vancomycin. V_d adjusted for IBW was found to be greater in obese patients than in normal patients, and the authors noted that female gender, older age and obesity all resulted in higher V_d through the use of regression equations. They recommend adjusting dose based on these factors. Another study by Leong *et al.* compared vancomycin clearance in overweight and obese patients to determine the best body weight measurement to use when dosing. However, only vancomycin troughs were available for assessment, and therefore, differences in V_d were not able to be assessed.[46] The authors concluded AdjBW was the best predictor of vancomycin clearance and serum concentrations. Finally, a study by Reynolds *et al.*[47] compared doses and serum drug concentrations before and after a change in the institution's vancomycin dosing protocol. The protocol was changed from 15 mg/kg every 8–12 h to either 10 mg/kg every 12 h or 15 mg/kg every 24 h in obese patients. This resulted in a lower adjusted maintenance dose for obese patients of 19 mg/kg/day in the new protocol as opposed to 34 mg/kg/day in the prior protocol. The authors found an increase in frequency of target trough attainment and below-target attainment and a reduced frequency of supratherapeutic troughs. The revised protocol with lower total daily doses improved target trough attainment with minimal nephrotoxicity (1·2%) utilizing ABW.

Vancomycin clearance and V_d have been shown to increase in obese patients, which correspond with the need for increased doses in larger patients. However, a retrospective study by Heble *et al.*[48] in a group of obese and non-obese paediatric patients showed obesity to be an independent risk factor for elevated steady-state troughs when receiving equivalent doses by ABW. Presently, studies utilizing AdjBW provide insufficient data to support its use, although they have shown a correlation between AdjBW and Cockroft–Gault-predicted creatinine clearance, which can correlate to drug clearance. Overall, dosing vancomycin based on ABW is likely appropriate for initial dosing recommendations followed by therapeutic drug concentration monitoring, but obese patients may have reduced clearance and therapeutic drug monitoring of vancomycin trough levels is encouraged.

REVIEW OF ANTIFUNGAL AGENTS

Amphotericin B

Amphotericin B pharmacokinetics in obesity has been evaluated in four animal studies, but there is currently no published literature in humans (Table 4). Amphotericin B has nonlinear kinetics, resulting in a large increase in serum levels compared to the magnitude of increase in dose.[49] The V_d for liposomal amphotericin B is relatively small and ranges from 0·1 to 0·16 L/kg in hemopoetic stem cell transplant recipients and patients with cancer, which suggest limited drug distribution into adipose tissue.

Vadieie *et al.*[50] studied amphotericin B disposition in the hyperlipidemic Zucker rat compared to lean littermates. Serial blood samples were obtained after a single 1·2 mg/kg dose and showed a twofold increase in AUC in obese rats. Weight-corrected V_d and total body clearance were significantly lower in the obese rats. There was a significant decline in creatinine clearance from baseline in obese rats, whereas lean rats showed no difference in renal function.

Another study performed in non-infected rabbits by Groll *et al.*[51] examined amphotericin B concentrations in various body tissues after administration of different drug formulations, including amphotericin B deoxycholate, amphotericin B colloidal dispersion, amphotericin B lipid complex or liposomal amphotericin B. Compared to bone marrow and the liver, accumulation in fat tissue was relatively poor with concentrations being 22% or less than that found in liver or bone marrow for all formulations tested. Authors suggest dosing obese patients based on LBW accounting for expanded blood volume.

Two additional studies examined amphotericin B in hypercholesterolaemic rabbits.[52,53] Ramaswamy *et al.* found that AUC was significantly higher and steady-state V_d was significantly lower in cholesterol-fed rabbits relative to regular diet-fed rabbits. Significant increases in plasma creatinine levels were also observed in both diet groups. Koldin *et al.* saw no difference in rabbit survival rates or elevations of creatinine levels between groups when comparing normal and hypercholesterolaemic rabbits. Rabbits in both studies had similar ABW between groups but differences in serum cholesterol levels.

Prescribing information recommends weight-based doses ranging from 3 to 6 mg/kg/day depending on indication for liposomal and lipid-based products, but no recommended maximum dose is suggested and use in obesity is not addressed.[49] Animal studies demonstrate significant increase in amphotericin B serum concentration in obese rats and rabbits with poor lipid distribution and increased rates of nephrotoxicity. Use of IBW or AdjBW could be considered when determining doses for morbidly obese patients depending on the indication for use. More aggressive dosing could be warranted in certain situations, and the limitations of utilizing animal data for human dosing recommendations should be acknowledged.

Flucytosine

Flucytosine pharmacokinetics in obesity have been described in one case report.[54] Flucytosine is small (129 Da), only 3–4% protein bound and has a modest V_d of approximately 0·6 L/kg in normal patients.[49] A case report discusses a morbidly obese female who received 0·3–0·5 mg/kg/day IBW for treatment of extrameningeal cryptococcal infection with resolution of infection. The patient had apparent CL of 1·5 and 0·71 mL/min/kg and V_d of 0·83 and 0·4 L/kg relative to IBW and ABW, respectively. The authors recommend use of IBW as opposed to ABW as the examined pharmacokinetic parameters seemed to correlate best with non-obese patients when standardized to IBW. The use of ABW for flucytosine dosing in obese patients in the absence of robust clinical data may be prudent – given its V_d – for initial dosing of life-threatening fungal infections, but therapeutic drug monitoring and individualized dosing are highly recommended. For non-life-threatening infections, doses based on IBW may be sufficient.

Voriconazole

Voriconazole pharmacokinetics in obesity have been examined in one small randomized trial, two retrospective studies and three case reports. The V_d for voriconazole is 4·6 L/kg and correlates with high tissue distribution.[55] The hepatic cytochrome P450 enzymes metabolize voriconazole and are the primary route of elimination.[55] Voriconazole metabolism is nonlinear, and serum concentrations are significantly increased following saturation of cytochrome P450 enzymes. Additionally, per cent plasma protein binding is 58%. The prescribing information recommends a loading dose of 6 mg/kg/dose IV every 12 h followed by 4 mg/kg/dose IV or 200 mg PO every 12 h, but dosing in obesity is not specifically addressed.

In 2011, a randomized, crossover study was performed in 16 obese and non-obese patients (mean BMI 46 and 24 kg/m^2, respectively).[56] Patients received either 400 mg of oral voriconazole every 12 h for two doses followed by 200 mg every 12 h for seven doses or 400 mg every 12 h for two doses followed by 300 mg every 12 h for seven doses. The authors found the V_d and clearance of the drug to be similar between weight groups; however, AUC was 50% greater in obese patients. The study suggests the use of LBW over ABW when dosing voriconazole in obese patients.

Two retrospective studies conducted support the use of AdjBW for dosing voriconazole. A retrospective review by Koselke *et al.*[57] compared voriconazole levels in obese and non-obese patients when given 4 mg/kg ABW doses. A significantly higher voriconazole trough concentration was observed in obese patients compared to non-obese patients (6·2 vs. 3·5 mg/L, $P > 0·0001$). The authors also compared dosing strategies in all obese patients who received dosing based on ABW, AdjBW and IBW. Mean serum trough concentrations in obese patients were 2·7, 3·2 and 6·2 mg/L when dosed by IBW, AdjBW and ABW, respectively ($P < 0·0001$). No obese patients dosed based on IBW or AdjBW experienced supratherapeutic levels. Therapeutic trough levels were achieved more often in patients dosed by IBW or AdjBW (60% and 67%, respectively) compared to ABW (28%). The authors concluded voriconazole should not be dosed based on ABW.[57] A retrospective chart review by Davies-Vorbrodt *et al.*[58] examined patients on voriconazole with documented serum concentrations stratified by BMI. Random voriconazole serum levels were significantly higher in patients with BMI of 25 kg/m^2 or more compared to those with lower BMI.[58] The authors recommend use of AdjBW when dosing voriconazole in obese patients.[58] The use of AdjBW has also been recommended in three different case studies, with two patients poor voriconazole metabolizers.[59–61]

Although available literature includes retrospective studies with small sample sizes, there is a strong association with

Table 4. Antifungal agents

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Amphotericin B				
Disposition and toxicity of amphotericin B in the hyperlipidemic Zucker rat model Vadiei (1990)	• Zucker hyperlipidemic obese rat model • Serial blood samples after single IV infusion of amphotericin B (1·2 mg/kg) in hyperlipidemic obese rats compared with lean litter mates • n = 12	• AUC 15 600 vs. 7800 ng h/mL ($P < 0·05$) in obese and lean litter rats, respectively • No difference in elimination rate constants • Weight-corrected V_d 1·847 L/kg and 4·162 L/kg in obese and lean rats, respectively ($P < 0·05$) • Weight-corrected CL 0·087 and 0·177 L/h·kg in obese and lean rats, respectively ($P < 0·05$)	• Significant decline in creatinine clearance from baseline in obese rats coupled with increase in SCr whereas no differences found in lean rats	• Similarities in absolute pharmacokinetic variables and protein: lipoprotein ratios suggest differences in disposition and toxicity due to differences in lipoprotein-mediated transport mechanisms
Distribution of lipid formulations of amphotericin B into bone marrow and fat tissue in rabbits Groll (2000)	• Non-infected rabbit model • Daily 1 mg/kg IV amphotericin B deoxycholate or 5 mg/kg IV amphotericin B colloidal dispersion, lipid complex or liposomal amphotericin B for seven doses • n = 16	• Accumulation in fat tissue was relatively poor: 22% or less than that in liver or bone marrow for all formulations tested	• Not addressed	• Authors suggest dosing obese patients based on LBW plus a factor accounting for expanded blood volume
Amphotericin B lipid complex or amphotericin B multiple-dose administration to rabbits with elevated plasma cholesterol levels: pharmacokinetics in plasma and blood, plasma lipoprotein levels, distribution in tissue, and renal toxicities Ramaswamy (2001)	• Cholesterol-fed rabbit model • Plasma cholesterol concentration, severity of drug-induced renal toxicity and pharmacokinetics of amphotericin B in hypercholesterolaemic rabbits after 7 days of 1 mg/kg amphotericin B deoxycholate or lipid complex • n = 18	• Plasma AUC of 140·4 and 10·0 μg h/mL in cholesterol-fed compared to 35·3 and 2·6 μg h/mL in regular diet-fed rabbits for deoxycholate and lipid complex, respectively • V_d of 1·1 and 29 L/kg in cholesterol-fed compared to 4·4 and 50 L/kg in regular diet-fed rabbits for deoxycholate and lipid complex, respectively • Systemic clearance of 7·5 and 104 mL/h/kg in cholesterol-fed compared to 30·1 and 475 mL/h/kg in regular diet-fed rabbits for deoxycholate and lipid complex, respectively	• Renal toxicity following ABLC to cholesterol-fed rabbits is greater than when given to regular diet-fed rabbits (non-significant) • Significant increases in plasma creatinine levels observed in rabbits fed a cholesterol-enriched and regular diet when given amphotericin B	• Increase in plasma cholesterol modifies the pharmacokinetics of amphotericin B and renal toxicity following the administration of multiple doses of amphotericin B deoxycholate and lipid complex

(continued)

Table 4 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Effects of elevation of serum cholesterol and administration of amphotericin B complexed to lipoproteins on amphotericin B-induced toxicity in rabbits Koldin (1985)	• Rabbit hyperlipidemic diet-fed model • Amphotericin B 6·5 mg/kg infused into normal or hypercholesterolaemic (20-fold increase in serum cholesterol) rabbits • n = 20	• Total cholesterol values in serum rose from 43 to 923 mg/mL in hypercholesterolaemic group prior to amphotericin B administration	• No difference in survival rates or elevations of creatinine levels between groups	• Hypercholesterolaemia induced by diet does not influence the toxicity of amphotericin B in rabbits, and amphotericin B given with LDL is more toxic than if given alone
Flucytosine				
Flucytosine dosing in an obese patient with extrameningeal cryptococcal infection Gillum (1995)	• Case report • 31-year-old obese patient (BMI 45·9 kg/m^2) • Flucytosine dosed based on IBW with 0·3 mg/kg/day initially, then increased to 0·5 mg/kg/day	• Infection resolution • Apparent clearance of 1·5 and 0·71 mL/min/kg relative to IBW and ABW, respectively • V_d of 0·83 and 0·4 L/kg relative to IBW and ABW, respectively • Population estimates for clearance and V_d of 1–2 mL/min/kg and 0·5–0·9 L/kg, respectively; this patient seemed to correlate best with population estimates utilizing IBW as opposed to ABW	• No adverse drug events observed	• Case supports dosing utilizing IBW
Voriconazole				
Evaluation of the effect of obesity on voriconazole serum concentrations Koselke (2012)	• Retrospective • Comparison of voriconazole levels in obese and non-obese adult patients receiving voriconazole dosed at 4 mg/kg ABW • n = 87	• Mean serum voriconazole trough level 6·2 and 3·5 mg/L (P = 0·005) in obese patients compared to non-obese patients, respectively	• 3 non-obese and 1 obese patient with AST or ALT ≥5 times the upper limit of normal • Neurotoxicity did not differ between groups	• Voriconazole should not be dosed based on ABW in obese patients due to supratherapeutic concentrations

(continued)

Table 4 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Steady-state plasma pharmacokinetics of oral voriconazole in obese adults Pai (2011)	• Randomized, crossover study (7-day washout) in obese adults • Regimen 1: voriconazole 400 mg po q12h ×2 doses followed by 200 mg po q12h ×7 doses • Regimen 2: voriconazole 400 mg po q12h ×2 doses followed by 300 mg po q12h ×7 doses • n = 8	• V_d similar between obese and non-obese patients for both regimens • Regimen 1: $AUC_{0\rightarrow12}$ 14·6 and 9·76 mg/h·l in and apparent clearance 13·4 and 20 L/h in obese and non-obese patients, respectively • Regimen 2: AUC and clearance similar between obese and non-obese patients • Adjusted r^2 0·14, 0·31, 0·38, and 0·42 for linear regression of AUC by ABW, IBW, AdjBW and LBW, respectively	• Not evaluated	• Regimen 1: AUC greater in the obese patient, indicating that the dose should not be based on ABW • Higher correlation of AUC with LBW instead of ABW
Voriconazole serum levels in obese immunocompromised patients Davies-Vorbrodt (2013)	• Retrospective chart review • Patients who received voriconazole with serum concentrations on file • n = 92	• Median random serum concentrations in patients with BMI ≥ 25 vs. BMI < 25 for IV formulation were 6·4 and 2·8 mg/L, respectively (P = 0·04)	• Increasing serum concentration correlated with increase in ALT levels (P = 0·85, P = 0·011 for all concentrations; P = 0·97, P < 0·001 for random or trough concentrations)	• AdjBW dosing may be most appropriate in obese patients
Dosing voriconazole in an obese patient Dickmeyer (2011)	• Case report • 30-year-old male, BMI 84·5 kg/m^2 • Dosed by adjusted weight: 6 mg/kg q12h ×2 doses followed by 4 mg/kg q12h • AdjBW: (ABW − IBW) ×0·4 + IBW	• Steady-state AUC 41·85 mg h/L in case patient vs. reference of 14·75–47·83 mg h/L in other allogeneic stem cell transplant recipients	• Not addressed	• Adjusted weight yields voriconazole AUC similar to non-obese patients
Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype Moriyama (2011)	• Case report • 17-year-old male, BMI 35 kg/m^2 • Dosed 4·9 mg/kg q12h ×2 doses, then 4 mg/kg q12h ×4 days with ABW • AdjBW: (ABW − IBW) × 0·4 + IBW	• After 2·5 days using AdjBW, AUC 86·1 mg h/L, trough 8·2 μg/mL; after 8·5 days, trough increased to 5·8 μg/mL • CYP2C19 homozygous poor metabolizer per genotyping	• Voriconazole discontinued due to QTc prolongation	• Voriconazole does not distribute extensively into adipose tissue, and patients should be dosed on AdjBW

(continued)

Table 4 (continued)

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Prolonged half- life of voriconazole in a CYP2C19 homozygous poor metabolizer receiving vincristine chemotherapy: avoiding a serious adverse drug interaction Moriyama (2013)	• Case report • 41-year-old male, BMI 36 kg/m^2, CYP2C19 poor metabolizer • AdjBW = 0·3 (ABW − IBW) + IBW • Dosed 6 mg/kg IV q12h ×2 doses followed by 4 mg/kg q12h	• Steady-state trough of 6·1 μg/mL, AUC 77·79 mg h/L	• Reported tingling, numbness in fingertips	• Increased voriconazole $t_{1/2}$, reduced clearance required discontinuation of drug 3 days prior to vincristine chemotherapy

V_d, volume of distribution; BMI, body mass index; IBW, ideal body weight; ABW, actual body weight; AdjBW, adjusted body weight; LBW, lean body weight.

increased voriconazole concentrations in obese patients receiving ABW dosing. Empiric dosing based on AdjBW or IBW should be considered; however, adjustments should be made on a case-by-case basis depending on infection severity, and early therapeutic drug concentration monitoring is recommended.

REVIEW OF ANTIVIRAL AGENTS

Acyclovir

Acyclovir pharmacokinetics in obesity have not been evaluated in animal studies, but there are two case reports and one small human study (Table 5). Acyclovir is a small drug (225 Da) with low plasma protein binding (9–33%). Half-life and total body clearance are dependent on renal function, and acyclovir has a V_d of approximately 48 L/m^2.[62,63]

An abstract presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy in 1991 described a single-dose pharmacokinetics study in obese and non-obese patients.[64] The authors found that V_d in both groups was approximately 43 L, leading them to conclude that IBW should be utilized when dosing acyclovir in obesity.

Hernandez *et al.*[65] describe a 60-year-old obese male (BMI 37·6 kg/m^2) with suspected herpes encephalitis receiving acyclovir at roughly 9 mg/kg/dose ABW IV every 8 h. By day 3, serum creatinine and BUN significantly increased, which prompted a discontinuation of acyclovir. The patient was diagnosed with acyclovir-induced nephrotoxicity and acute renal failure. Efficacy of treatment could not be assessed as herpes encephalitis was ultimately ruled out and the patient was lost to follow-up. Another case report involved a 23-year-old morbidly obese male with suspected viral encephalitis given acyclovir 10 mg/kg/dose ABW IV every 8 h.[66] Within 48 h, renal function deteriorated and acyclovir was discontinued.

Based on recommendations from the manufacturer's prescribing information, as well as these the limited literature, weight-based treatment dosing of acyclovir should be based on IBW.[67]

Cidofovir

Cidofovir pharmacokinetics in obesity have not been evaluated in animal studies, and no published literature in human patients currently exists. The average V_d when given with probenecid is 0·41 L/kg, and <6% of the drug is bound to serum proteins.[68] It is a small drug at 315 Da. No recommendations for dosing in obesity exist in the prescribing information, but pharmacokinetic values in non-obese patients suggest limited distribution into adipose tissue. As a result, decisions regarding the appropriate weight to use when calculating cidofovir dose should be made on a case-by-case basis while balancing risk vs. benefit.

Foscarnet

Foscarnet pharmacokinetics in obesity have not been evaluated in animal or human subjects. It is a small (300 Da), hydrophilic agent and in non-obese adults has a V_d of 0·4–0·5 L/kg, protein binding of 14–17% and is primarily eliminated via the kidney.[69] Recommendations are not provided in the prescribing information regarding dosing in obese patients. Due to its hydrophilic nature, major risk of nephrotoxicity and other adverse effects, it may be prudent to utilize IBW or AdjBW.

Table 5. Antiviral agents

Title & Author (year)	Design & sample size	Results	Safety	Conclusions
Acyclovir				
Acyclovir pharmacokinetics in morbid obesity Davis (1991)	• Single-dose pharmacokinetic study • Acyclovir 5 mg/kg × ABW • n = 12	• Steady-state V_d was 0·74 and 0·42 L/kg ABW in non-obese and obese patients, respectively	• Not addressed	• Use of IBW appropriate when dosing in obesity
Acyclovir-induced renal failure in an obese patient Hernandez (2009)	• Case report • 60-year-old male (BMI 37·6 kg/m^2) with possible herpes encephalitis • Acyclovir dosed 9·2 mg/kg/dose × ABW IV every 8 h	• Serum creatinine and BUN rose on day 3, and acyclovir was discontinued	• Patient developed acyclovir-induced nephrotoxicity	• Use of ABW for dosing acyclovir in an obese patient resulted in acute renal failure • True herpes infection was ruled out, preventing assessment of efficacy
Acyclovir-induced acute renal failure and the importance of an expanding waistline Seedat (2012)	• Case report • 23-year-old morbidly obese male with suspected viral encephalitis/meningitis • Acyclovir dosed 10 mg/kg/dose × ABW IV every 8 h	• Within 48 h of initiation, renal function deteriorated • Patient returned to baseline renal function when acyclovir was discontinued	• Patient developed acyclovir-induced nephrotoxicity (reversible)	• ABW in obese patient resulted in acute reversible renal failure • Antibiotic therapy withdrawn after no proof of infectious aetiology

BMI, body mass index; ABW, actual body weight.

Table 6. UMHS weight-based dosing recommendations for intravenous antimicrobials in adult morbidly obese patients

If BMI ≥ 35 kg/m^2, use AdjBW when calculating dose
- Voriconazole
- Daptomycin
- Ganciclovir (intravenous)[a]
- Trimethoprim/sulfamethoxazole (intravenous)[a]
- Foscarnet[a]

If BMI ≥30 kg/m^2, use IBW when calculating dose
- Colistimethate
- Acyclovir (intravenous)

Calculations
- IBW for men (kg) = [2·3 × (height in inches − 60)] + 50
- IBW for women (kg) = [2·3 × (height in inches − 60)] + 45·5
- AdjBW (kg) = [(ABW − IBW) × 0·4] + IBW

UMHS, University of Michigan Health System; BMI, body mass index; IBW, ideal body weight; ABW, actual body weight; AdjBW, adjusted body weight.
[a]Recommendations are based on pharmacologic or pharmacokinetic data, and there are no published clinical studies at the time of this review. Patients should be monitored closely for clinical response and toxicity.

Ganciclovir

Ganciclovir pharmacokinetics in obesity have not been evaluated in animal or human subjects. In non-obese adults, ganciclovir has a steady-state V_d of 0·74 L/kg, and binding to plasma proteins is minimal at 1–2%, which is similar to acyclovir.[70] Dosing in obese patients is not addressed in the prescribing information. Due to the hydrophilic nature of ganciclovir and its similarity in size (277 Da), action and toxicity to acyclovir, utilization of IBW when calculating doses in obese patients could be considered on a case-by-case basis.

UMHS DOSING RECOMMENDATIONS AND COST ANALYSIS

In the summer of 2012, UMHS implemented a weight-based antimicrobial dosing guideline for select antimicrobials in morbidly obese patients (Table 6). The recommendations were developed following extensive literature review and expert opinion for the following antimicrobials: colistimethate, daptomycin, trimethoprim/sulfamethoxazole, acyclovir, foscarnet, ganciclovir and voriconazole. The Pharmacy and Therapeutics Committee approved the guideline, which recommends using AdjBW for patients with BMI ≥35 kg/m^2 for daptomycin, trimethoprim/sulfamethoxazole, foscarnet, ganciclovir, and voriconazole and IBW when calculating the dose for acyclovir and colistimethate. The recommendations were posted on the internal antimicrobial stewardship website, and pharmacists were provided a copy of the recommendations. Pharmacists were encouraged to recommend dose adjustments for obese patients upon order verification or during daily patient rounds, but there were no prompts built into our computerized physician order entry system during this timeframe.

Table 7. Compliance and cost savings following UMHS dosing in obesity guideline implementation (November 2012–November 2013)

Drug	Per cent compliance with guideline (N[a])	Annual savings[b]	Additional savings[b] potential
Acyclovir	68 (141/198)	$577	$424
Daptomycin	64 (505/705)	$89 667	$26 155
Ganciclovir	50 (33/44)	$454	$348
TMP/SMZ	50 (57/130)	$862	$753
Voriconazole	53 (18/33)	$1771	$2054
Colistimethate	100 (11/11)	$4554	$0
Total	68 (765/1121)	$97 886	$29 733

TMP/SMZ, trimethoprim/sulfamethoxazole; UMHS, University of Michigan Health System.
[a]Number of doses dispensed.
[b]Savings based on average wholesale price (rounded to nearest dollar).

Compliance with dosing recommendations and cost analysis were performed for all morbidly obese patients (BMI > 35 kg/m^2) receiving weight-based dosing of antimicrobials for a 1-year period (November 2012 through November 2013). Compliance with the guideline recommendations occurred in 64% of doses dispensed, which resulted in an annual antimicrobial cost savings of $97 886, based on average wholesale price (Table 7). If 100% compliance with the guideline was attained, an additional savings potential of $29 733 would be achieved. Efficacy and safety were not evaluated.

WHAT IS NEW AND CONCLUSION

Optimal antimicrobial dosing in obese patients continues to present challenges. Most current publications are pharmacokinetic studies with limited data evaluating clinical efficacy and toxicity. However, morbidly obese patients have altered pharmacokinetic properties for most weight-based antimicrobials compared to normal-weight patients. Providing adjusted-dose weight-based antimicrobial dosing in morbidly obese patients may help maximize efficacy, minimize toxicity and provide antimicrobial cost savings. However, clinical judgment should always be used when making dose adjustments in obese patients, particularly for agents with scarce available literature in obese patients.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

SOURCE OF FUNDING

No funding to disclose.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010. *NCHS Data Brief*, 2012;**82**:1–8.
2. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur J Clin Pharmacol*, 1983;**24**:643–647.

3. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest*, 2002;**122**:1256–1263.
4. Mancuso P. Obesity and respiratory infections: does excess adiposity weigh down host defense? *Pulm Pharmacol Ther*, 2013;**26**:412–419.
5. Falagas ME, Kompoti M. Obesity and infection. *Lancet Infect Dis*, 2006;**6**:438–446.
6. Jain R, Chung SM, Jain L *et al.* Implications of obesity for drug therapy: limitations and challenges. *Clin Pharmacol Ther*, 2011;**90**:77–89.
7. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*, 2010;**49**:71–87.
8. Benedek IH, Fiske WD III, Griffen WO, Bell RM, Blouin RA, McNamara PJ. Serum alpha 1-acid glycoprotein and the binding of drugs in obesity. *Br J Clin Pharmacol*, 1983;**16**:751–754.
9. Brill MJ, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CA. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet*, 2012;**51**:277–304.
10. Aggarwal N, Porter AC, Tang IY, Becker BN, Akkina SK. Creatinine-based estimations of kidney function are unreliable in obese kidney donors. *J Transplant*, 2012;**2012**:872894.
11. Hites M, Taccone FS, Wolff F *et al.* Case–-control study of drug monitoring of beta-lactams in obese critically ill patients. *Antimicrob Agents Chemother*, 2013;**57**:708–715.
12. Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pasculle AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J Infect Dis*, 1978;**138**:499–505.
13. Blouin RA, Mann HJ, Griffen WO Jr, Bauer LA, Record KE. Tobramycin pharmacokinetics in morbidly obese patients. *Clin Pharmacol Ther*, 1979;**26**:508–512.
14. Pai MP, Nafziger AN, Bertino JS Jr. Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. *Antimicrob Agents Chemother*, 2011;**55**:4006–4011.
15. Korsager S. Administration o gentamicin to obese patients. *Int J Clin Pharmacol Ther Toxicol*, 1980;**18**:549–553.
16. Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. *J Clin Pharmacol*, 1981;**21**:288–293.
17. Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM. A standard weight descriptor for dose adjustment in the obese patient. *Clin Pharmacokinet*, 2004;**43**:1167–1178.
18. Bauer LA, Blouin RA, Griffen WO Jr, Record KE, Bell RM. Amikacin pharmacokinetics in morbidly obese patients. *Am J Hosp Pharm*, 1980;**37**:519–522.
19. Gibbs RS, Blanco JD, Lipscomb KA. Aminoglycoside dosing in obese puerperal women. *Am J Obstet Gynecol*, 1985;**152**:89–90.
20. Blouin RA, Brouwer KL, Record KE, Griffen WO Jr, Plezia PM, John W. Amikacin pharmacokinetics in morbidly obese patients undergoing gastric-bypass surgery. *Clin Pharm*, 1985;**4**:70–72.
21. Ortega A, Aldaz A, Giraldez J, Brugarolas A. Relationship between pharmacokinetic parameters of gentamicin and patient characteristics and/or clinical data in patients with solid organ tumours. *Pharm World Sci*, 1999;**21**:227–232.
22. *Tobramycin*. Schaumburg, IL: APP Pharmaceuticals, LLC, 2008.
23. Pogue JM, Lee J, Marchaim D *et al.* Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis*, 2011;**53**:879–884.
24. Deryke CA, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. *Antimicrob Agents Chemother*, 2010;**54**:4503–4505.
25. Gauthier TP, Wolowich WR, Reddy A, Cano E, Abbo L, Smith LB. Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. *Antimicrob Agents Chemother*, 2012;**56**:2392–2396.
26. Garonzik SM, Li J, Thamlikitkul V *et al.* Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother*, 2011;**55**:3284–3294.
27. Elwood CM, Lucas GD, Muehrcke RC. Acute renal failure associated with sodium colistimethate treatment. *Arch Intern Med*, 1966;**118**:326–334.
28. *Cubicin (daptomycin)*. Lexington, MA: Cubist Pharmaceuticals, Inc., 2013.
29. Pai MP, Norenberg JP, Anderson T *et al.* Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. *Antimicrob Agents Chemother*, 2007;**51**:2741–2747.
30. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched non-obese subjects. *J Clin Pharmacol*, 2005;**45**:48–56.
31. Bubalo JS, Munar MY, Cherala G, Hayes-Lattin B, Maziarz R. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. *Antimicrob Agents Chemother*, 2009;**53**:428–434.
32. Pea F, Cojutti P, Sbrojavacca R *et al.* TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. *Ann Pharmacother*, 2011;**45**:e37.
33. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*, 2010;**50**:1568–1574.
34. Bookstaver PB, Bland CM, Qureshi ZP *et al.* Safety and effectiveness of daptomycin across a hospitalized obese population: results of a multicenter investigation in the southeastern united states. *Pharmacotherapy*, 2013;**33**:1322–1330.
35. Ng J, Schulz L, Rose W et al. Daptomycin dosing based on ideal body weight versus actual body weight: comparison of clinical outcomes. *Antimicrob Agents Chemother*, 2014;**58**:88–93.
36. *Synercid (quinupristin and dalfopristin)*. Greenville, NC: DSM Pharmaceuticals, Inc., 2012.
37. Lefebvre P, Rey J, Morganroth J, Geary W, Montay G. Open, comparative, study of the safety of a single dose of quinupristin/dalfopristin (Q/D, RP 59500) in obese and in non-obese male subjects. *20th International Congress of Chemotherapy, Sydney, Australia*, 1997, Organising Committee, Vic., Australia.
38. *Bactrim (sulfamethoxazole and trimethoprim DS)*. Philadelphia, PA: AR Scientific, Inc., 2013.
39. Garrett ER, Suverkrup RS, Eberst K, Yost RL, O'Leary JP. Surgically affected sulfisoxazole pharmacokinetics in the morbidly obese. *Biopharm Drug Dispos*, 1981;**2**:329.
40. Baxter Healthcare Corporation, ed. *Vancomycin hydrochloride [package insert]*. Deerfield, IL: Baxter Healthcare Corporation, 2011.
41. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. *Eur J Clin Pharmacol*, 1998;**54**:621–625.
42. Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a bayesian forecasting technique. *Antimicrob Agents Chemother*, 1993;**37**:436–440.
43. Penzak SR, Gubbins PO, Rodvold KA, Hickerson SL. Therapeutic drug monitoring of vancomycin in a morbidly obese patient. *Ther Drug Monit*, 1998;**20**:261–265.

44. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. *Antimicrob Agents Chemother*, 1982;**21**:575–580.
45. Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. *Ther Drug Monit*, 1994;**16**:513–518.
46. Leong JV, Boro MS, Winter M. Determining vancomycin clearance in an overweight and obese population. *Am J Health Syst Pharm*, 2011;**68**:599–603.
47. Reynolds DC, Waite LH, Alexander DP, DeRyke CA. Performance of a vancomycin dosage regimen developed for obese patients. *Am J Health Syst Pharm*, 2012;**69**:944–950.
48. Heble DE Jr, McPherson C, Nelson MP, Hunstad DA. Vancomycin trough concentrations in overweight or obese pediatric patients. *Pharmacotherapy*, 2013;**33**:1273–1277.
49. *AmBisome (amphotericin B)*. Northbrook, IL: Astellas Pharma US, Inc., 2012.
50. Vadiei K, Lopez-Berestein G, Luke DR. Disposition and toxicity of amphotericin-B in the hyperlipidemic zucker rat model. *Int J Obes*, 1990;**14**:465–472.
51. Groll AH, Mickiene D, Piscitelli SC, Walsh TJ. Distribution of lipid formulations of amphotericin B into bone marrow and fat tissue in rabbits. *Antimicrob Agents Chemother*, 2000;**44**:408–410.
52. Koldin MH, Kobayashi GS, Brajtburg J, Medoff G. Effects of elevation of serum cholesterol and administration of amphotericin B complexed to lipoproteins on amphotericin B-induced toxicity in rabbits. *Antimicrob Agents Chemother*, 1985;**28**:144–145.
53. Ramaswamy M, Peteherych KD, Kennedy AL, Wasan KM. Amphotericin B lipid complex or amphotericin B multiple-dose administration to rabbits with elevated plasma cholesterol levels: pharmacokinetics in plasma and blood, plasma lipoprotein levels, distribution in tissues, and renal toxicities. *Antimicrob Agents Chemother*, 2001;**45**:1184–1191.
54. Gillum JG, Johnson M, Lavoie S, Venitz J. Flucytosine dosing in an obese patient with extrameningeal cryptococcal infection. *Pharmacotherapy*, 1995;**15**:251–253.
55. Pfizer Inc. ed. *Vfend*. New York, NY: Pfizer, Inc., 2011.
56. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. *Antimicrob Agents Chemother*, 2011;**55**:2601–2605.
57. Koselke E, Kraft S, Smith J, Nagel J. Evaluation of the effect of obesity on voriconazole serum concentrations. *J Antimicrob Chemother*, 2012;**67**:2957–2962.
58. Davies-Vorbrodt S, Ito JI, Tegtmeier BR, Dadwal SS, Kriengkauykiat J. Voriconazole serum concentrations in obese and overweight immunocompromised patients: a retrospective review. *Pharmacotherapy*, 2013;**33**:22–30.
59. Moriyama B, Falade-Nwulia O, Leung J *et al.* Prolonged half-life of voriconazole in a CYP2C19 homozygous poor metabolizer receiving vincristine chemotherapy: avoiding a serious adverse drug interaction. *Mycoses*, 2011;**54**:e877–e879.
60. Moriyama B, Jarosinski PF, Figg WD *et al.* Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype. *Pharmacotherapy*, 2013;**33**:e19–e22.
61. Dickmeyer NJ, Kiel PJ. Dosing voriconazole in an obese patient. *Clin Infect Dis*, 2011;**53**:745.
62. Blum MR, Liao SHT, Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. *Am J Med*, 1982;**73** (Suppl 1A):186.
63. Laskin O. CLinical pharmacokinetics of acyclovir. *Clin Pharmacokinet*, 1983;**8**:187.
64. Davis R, Quenzer R, Weller S, Blum R. Acyclovir pharmacokinetics in morbid obesity. *Programs and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology, 1991.
65. Hernandez JO, Norstrom J, Wysock G. Acyclovir-induced renal failure in an obese patient. *Am J Health Syst Pharm*, 2009;**66**:1288–1291.
66. Seedat A, Winnett G. Acyclovir-induced acute renal failure and the importance of an expanding waist line. *BMJ Case Rep*, 2012;**2012**:1–3.
67. *Zovirax (acyclovir sodium)*. Research Triangle Park, NC: GlaxoSmithKline, 2003.
68. *Vistide (cidofovir injection)*. Foster City, CA: Gilead Sciences, Inc., 2000.
69. *Foscavir (foscarnet sodium)*. Wilmington, DE: AstraZeneca, 2012.
70. *Cytovene (ganciclovir sodium for injection)*. Nutley, NJ: Roche Laboratories, Inc., 2006.