Chapter 2
Penicillins

Iain J. Abbott and Kelly A. Cairns

Abstract Penicillins are among the most widely used class of antibiotics, utilised for a wide variety of clinical indications, including critical illnesses and sepsis. Clinical efficacy and the prevention of the emergence of resistance are critically dependent upon the correct dosing strategy in order to meet the required time-dependent pharmacodynamic target. Penicillins mainly experience increases in volume of distribution and renal clearance in obese patients, such that standard doses may not be sufficient to achieve target attainment. The dosing recommendation for penicillin antibiotics in obesity is, however, complex and lacking clinical evidence. This chapter will review the current literature and make suggestions for altered dosing for commonly prescribed penicillin antibiotics. Fortunately, given the relative safety profile of the penicillin antibiotics, greater flexibility at upper range of the dosing schedule, or frequency of administration, is available. Strategies such as extended and continuous infusions are explored, together with reference to front-loading dosing, therapeutic drug monitoring and Bayesian estimation techniques and software to promote individualised drug dosing. Critical illness in obese patients warrants careful consideration of penicillin dosing and must take into consideration the pharmacokinetic and pharmacodynamic changes and altered targets.

Keywords Penicillin · Obesity · Extended infusion · Continuous infusion · Pharmacokinetics · Pharmacodynamics

I.J. Abbott (✉)
Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia
e-mail: iainabbott@gmail.com

K.A. Cairns
Department of Pharmacy, Alfred Hospital, Melbourne, Australia

S.T.R. Zaidi and J.A. Roberts (eds.), *Drug Dosing in Obesity*,
DOI 10.1007/978-3-319-44034-7_2

Introduction

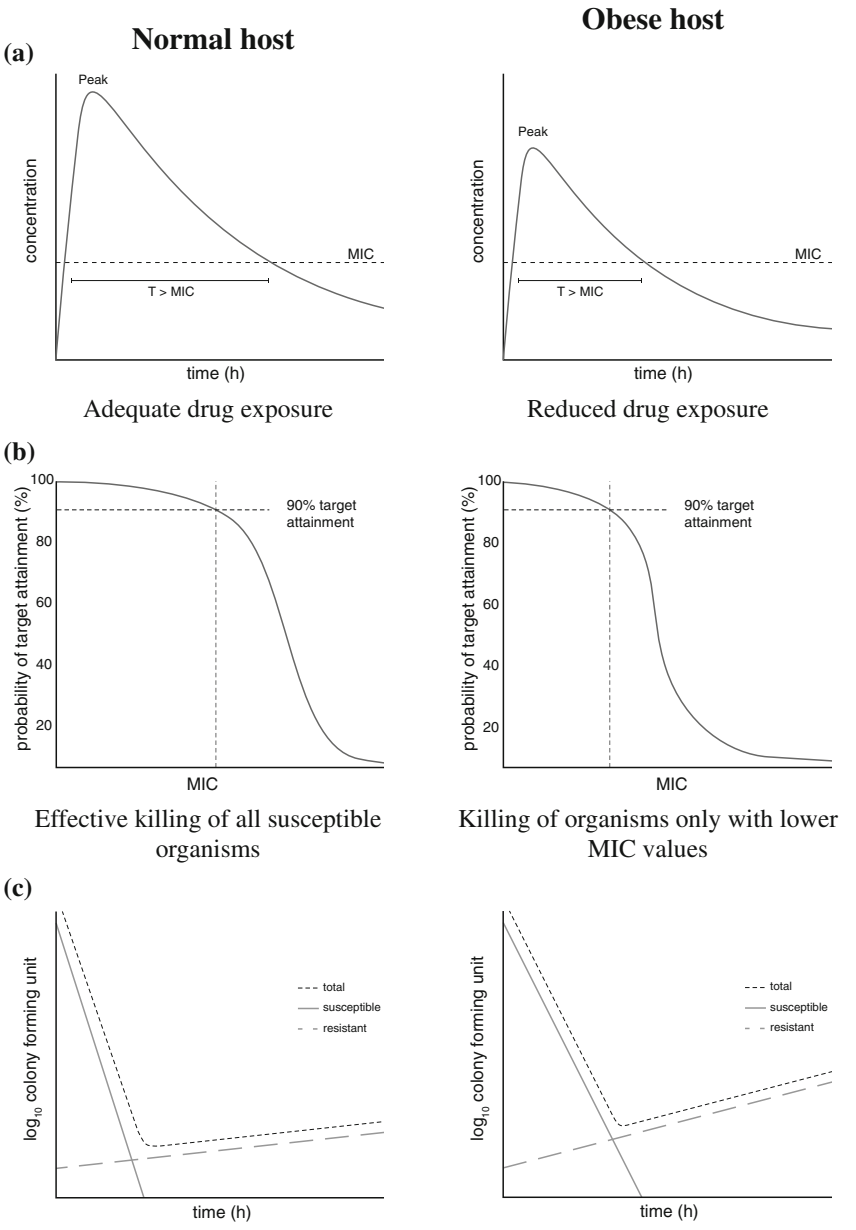
Penicillins represent the oldest class of antibiotics, since their discovery in 1928, and have been in clinical use since the 1940s. Over the years, this class of beta-lactams has expanded from the narrow spectrum penicillins, to combinations with beta-lactamase inhibitors, providing a broad spectrum of activity [1]. Narrow spectrum penicillins, such as intraveneous benzylpenicillin (penicillin G), intramuscular procaine penicillin and benzathine penicillin, and oral phenoxymethylpenicillin (penicillin V), are mainly active against Gram-positive organisms, but are inactivated by beta-lactamase enzymes. Despite their narrow spectrum, these penicillins remain the treatment of choice for many infections, including *Streptococcus pyogenes*, pneumococcal pneumonia, and syphilis. Antistaphylococcal pencillins, dicloxacillin and flucloxacillin, are stable to beta-lactamases, and are the standard of care for infections caused by methicillin-susceptible *Staphylococcus aureus*. The aminopenicillins, amoxycillin and ampicillin, have a relatively narrow spectrum of activity against susceptible Gram-negative pathogens, such as *Escherichia coli*, which is the most common urinary tract pathogen, but are again inactivated by strains that produce beta-lactamase enzymes. Broad-spectrum penicillins, piperacillin and ticarcillin, have an expanded spectrum that includes *Pseudomonas aeruginosa* species. The combination of a penicillin antibiotic and a beta-lactamase inhibitor, such as clavulanate and tazobactam, which in themselves have little inherent antibacterial activity, inhibit the enzymes produced by a variety of Gram-positive, Gram-negative and anaerobic bacteria. In combination, amoxycillin and ticarcillin with clavulanate, and piperacillin with tazobactam, the spectrum of activity is significantly expanded. Piperacillin-tazobactam (TZP) is currently a standard of care as empiric therapy for a number of critical infections, such as febrile neutropenia [2, 3], ventilator associated pneumonia [4], and severe diabetic foot infections [5]. All currently available penicillin antibiotics are vulnerable to expanded resistance mechanisms, either newly acquired or intrinsic in some organisms. Extended-spectrum beta-lactamases (e.g. $bla_{\text{CTX-M}}$), cephalosporinases (e.g. AmpC-type bla_{CMY}) and carbapenamases (e.g. metallo beta-lactamases, bla_{KPC}, and bla_{OXA}) all potentially inactivate antibiotics in the penicillin class. Despite their longstanding and widespread use, very little information is available about dosing in patients with an increased body-mass-index (BMI) for the class as a whole. Given that the penicillin class of antibiotics are frequently used in critical illness, where time to adequate antibiotic exposure is critical for survival, more studies are required to further understand the true impact of obesity on the pharmacokinetic/pharmacodynamic (PK/PD) targets, together with clinical outcomes.

Pharmacodynamic Target

Penicillins, like other beta-lactam antibiotics, display time-dependent pharmacodynamics (PD) (see Fig. 2.1, panel a). The antibiotic activity is due to inhibition of bacterial cell wall synthesis, which occurs over time to result in a relatively slow bactericidal action [6]. Bacterial kill and efficacy correlates best with the length of time (fT) that free (unbound) serum concentrations of the drug exceeds the organism's minimum inhibitory concentration (MIC) (i.e. $fT_{>MIC}$) [7]. Maximal organism kill occurs when drug concentrations are maintained at four-times the MIC [8]. The target for penicillin antibiotics is $fT_{>MIC}$ of roughly 50 % of the dosing schedule [9]. A post antibiotic effect is seen against Gram-positive organisms, but is minimal against Gram-negatives [10], thereby suggesting Gram-negative infections would benefit from a higher percentage $fT_{>MIC}$. Penicillins are also affected by an inoculum effect, such that infections with a high bacterial density require higher antibiotic concentrations, for longer durations, to inhibit growth [10]. In the setting of concurrent immunosuppression or critical illness a $fT_{>MIC}$ target approaching 100 % has been suggested [11]. In clinical practice, the MIC of the infecting organism is often not known at the time antibiotics are started, such that empiric dosing is required to cover organisms with a range of MICs, including those at the higher end of the susceptible range. Adequate drug exposure is also critical to prevent the emergence of resistance within an organism population [12], factoring in also the impact of the inoculum size, the duration of therapy and the presence of immune dysfunction [13].

Pharmacokinetic Changes in Obesity

Penicillins are hydrophilic antibiotics that are essentially eliminated by renal clearance, have a low volume of distribution (V) and a lower intracellular and tissue penetration [14]. The summary of expected changes in the PK of penicillins to be seen in obesity is presented in Table 2.1. Penicillins mainly experience increases in V and renal/creatinine clearance (CrCl) in obese patients, suggesting that standard doses may not be sufficient to achieve target attainment (50 % $fT_{>MIC}$), especially for bacteria with higher MICs (see Fig. 2.1, panel b). Despite applying adjusted body weight (ABW) and/or lean body weight (LBW) as size descriptors for dose adjustment for hydrophilic medications, an assessment of individual's calculated BMI and how that relates to the changes in the PK of the penicillins is more complex. Individuals with a raised BMI will not only have an increase in adipose tissue but also variable amounts of concurrent increases in lean muscle weight and blood volume. An elite athlete with a BMI $\geq$ 30 kg/m^2, for example, who has a large proportional increase in lean muscle mass, will have vastly different penicillin antibiotic PK changes compared with an individual with the same BMI but whose excess weight is predominantly made up of an increase in adipose tissue. This



Adequate drug exposure

Reduced drug exposure

Effective killing of all susceptible organisms

Killing of organisms only with lower MIC values

Effective suppression of resistant subpopulation by rapid kill and normal functioning immune system

Potential for re-growth of resistant sub-population by slower kill and obesity-related impaired immune system

◀ **Fig. 2.1** Schematic representation of the potential changes in PK/PD seen in obesity. Figure adapted from [9, 11]. *Panel a* Time-concentration curves. In the obese host there can be a reduced peak concentration due to the increased V, although obesity-related reduction in protein binding may counteract this for heavily protein-bound drugs such as di/flucloxacillin. Augmented renal/creatinine clearance accounts for a steeper clearance curve. Both factors impact on the $fT_{>MIC}$. *Panel b* MIC-target attainment curves. There is a quicker drop off in the percentage target attainment in the obese host as the organism becomes more resistant (i.e. increasing MIC). *Panel c* Time-organism re-growth curves. A theoretical risk of the emergence of a resistant sub-population during antibiotic treatment course. This is not only impacted upon by the reduction in $fT_{>MIC}$ but also the impact of immune dysregulation seen in obesity that would normally assist the antibiotic in organism kill

Table 2.1 Overview of penicillins ppharmacokinetic (PK) changes in obesityObesity

PK parameter	Effect of obesity
Absorption	
Oral Intramuscular Intravenous	Minimal change Avoid No change
Distribution	
Protein binding Volume of distribution	Reduced[a] Increased
Metabolism	No change
Excretion	Increased[b] (augmented renal/creatinine clearance)

[a]Results in an increase in the unbound penicillin concentrations, contributing to increased clearance

[b]Occurs in the absence of co-morbidities impacting on renal function

differentiation is important when dosing penicillins given the potential that the degree of increase in V may be unrecognized, which in turn has the potential to result in decreased plasma drug concentrations.

Review of Existing Literature

There is a dearth of clinical PK/PD studies examining dosing of penicillin antibiotics in obesity, and much of the more recent literature deals only with TZP (see Table 2.2). When compared to parameters in reference populations [1, 15, 16], there are consistent reports of increases in V and CrCl in obese subjects who have been administered TZP. In the critically ill cohort, however, it seems that severe sepsis alters the PK/PD more than obesity alone [17]. Similarly, renal function and the use of continuous renal replacement therapy have a large impact on PK/PD targets. In general, the doses of TZP studied were either at the upper end of the recommended dosing schedule (e.g. 4.5 g 6-hourly, 30 min infusion), or utilised extended infusions over 4 h.

Table 2.2 Piperacillin-tazobactam (TZP) pharmacokinetic/pharmacodynamic (PK/PD) changes in obesity: review of the literature

Study	No.	BMI (mean)	V	CrCl	t½	Dose (infusion time)	Comments
Reference population [15, 16, 56–58]			8.2–15.8 L	8.0–14.5 L/h	0.6–1.1 h	4.5 g (30 min)	
Sturm et al. (2014) [59]	9	57 kg/m^2	31.0 L	6.0 L/h	3.7 h	4.5 g Q6H (30 min)	Surgical ICU patients. Despite altered PK, use of high-dose TZP was appropriate (%$T_{>MIC}$ 100 % for all patients, MIC = 16 mg/L)
Hites et al. (2014) [58]	31	36 kg/m^{2a}	31.4 L	8.9 L/h	2.2 h	4.5 g Q8H (30 min)	Non-critically ill patients. Augmented renal/creatinine clearance (CrCl > 80 ml/min) responsible for low serum concentrations (V 26.9 L, CrCl 13.1 L/h, t½ 1.5 h). Standard dose was inadequate to treat less susceptible bacteria
Hites et al. (2013) [17]	49	40 kg/m^2	29.6 L	5.4 L/h	3.2 h	Daily dose 16 g (na)	Critically ill patients; obese vs. non-obese. No differences in PK. Only 47 % TZP drug levels were adequate. CRRT a risk factor for overdosage. CrCl: CRRT 4.5 L/h; without CRRT 10 L/h
Cheatham et al. (2013) [60]	14	52.3 kg/m^2	33.4 L	13.7 L/h	1.9 h	4.5 g/6.75 g Q8 H (4 h)	Hospitalized patients. Extend infusions provide target attainment of >90 % for pathogens with MICs $\leq$ 16 ug/mL
Zakrison et al. (2012) [49]	23	37 kg/m^{2b}	na	na	na	3.375 g Q6 H (na)	Complicated intra-abdominal infections. Post hoc analysis. Trend towards a lower cure rate in the high BMI group receiving TZP
Demam et al. (2012) [61]	1	55 kg/m^2	33 L	21 L/h	1.1 h	4.5 g Q6H (30 min)	Case report. Surgical site infection. PK/PD targets for a MIC 8 mg/L: %$T_{>MIC}$ 60 % and %$T_{>4xMIC}$ 25 %
Newman et al. (2007) [56]	1	50 kg/m^2	54.3 L	26.6 L/h	1.4 h	3.375 g Q4H (30 min)	Case report. Cellulitis. Achieved piperacillin %$T_{>MIC}$ 90.9 % for the cultured *P. aeruginosa* with MIC 8.0 mg/L

V volume of distribution; *CrCl* clearance; t½ half-life; *MIC* Minimum inhibitory concentration; *BMI* Body mass index

[a]Includes 14 patient who received meropenem and 11 patients who received cefepime

[b]Includes 32-patients who were randomised to receive ertapenem

For penicillin antibiotics that have been administered via the intravenous route, the impact of obesity on absorption should be minimal. The impact of obesity on oral penicillin absorption is also largely unaffected by obesity [18, 19]. Miskowiak et al. determined that in a small cohort of eight female patients, the absorption of phenoxymethypenicillin was no different before and three months after gastroplasty [20]. The absorption of phenoxymethylpenicillin and flucloxacillin is impaired by the presence of food in the stomach, and patients should be appropriately counseled by their pharmacist on the correct administration. For the remaining oral penicillin antibiotics, the increased splanchnic blood flow and delayed gastric emptying should also have minimal effects on absorption [21, 22]. Intramuscular administration represents a small proportion of penicillin administration. Where possible, the intramuscular administration of penicillins, such as benzathine penicillin and procaine penicillin, should be avoided in obese patients. Inadvertent administration of penicillin antibiotics into subcutaneous tissue, also known as 'intralipomatous' injections [23], may cause pain, altered absorption kinetics and potential tissue necrosis. General recommendations for tissue damage associated with the extravasation of injectable medications include those with a pH below 5.5 or greater than 8.5. The pH of both benzathine pencillin and procaine penicillin is reported to be between 5 and 7.5 [24].

The impact of obesity on the distribution of penicillin antibiotics represents a complex dilemma and is dependent on a number of variables. Penicillin antibiotics are generally hydrophilic [19, 25] and their V is generally low [26]. As such, they have poor distribution into adipose tissue [19]. Excess weight associated with obesity also includes increased lean mass to carry the adipose tissue thereby, providing an increased V for penicillin drugs [18, 19]. Kampmann et al. [27] reported a higher V for ampicillin in a small cohort of patients prior to gastric bypass surgery (0.60 L/kg, in patients with an average weight of 131 kg) compared to the same patients one year later when they were on average 44 kg lighter (V of 0.41 L/kg). Yuk et al. [28] measured nafcillin serum levels in a single morbidly obese (162 kg) endocarditis patient, and also identified an increased volume of distribution. Based on this, the authors were able to provide nafcillin dosing recommendations in obese patients. The predicted proportion of plasma protein binding of the penicillin antibiotics in the standard population varies markedly from 20 % for ampicillin to up to 93 % for flucloxacillin, although there are significant differences between measured and predicted unbound drug concentrations for the highly protein-bound beta-lactams [29]. The increased levels of lipoproteins, cholesterol and free fatty acids observed in obese patients has the potential to bind to serum proteins, such as albumin [19]. Suh et al. demonstrated that high levels of free fatty acids significantly reduced the protein binding of dicloxacillin, but increased the protein binding of benzylpenicillin [30]. As the free concentration of drug is responsible for therapeutic effects, a reduction in the availability of albumin increases the free concentration of the penicillin. In this previous work by Suh et al. there was a fivefold increase in the free dicloxacillin fraction and a 50 % reduction in the free fraction of benzylpenicillin observed [30]. The increase in free fraction of a protein-bound antibiotic will increase the peak penicillin concentration, but more

importantly, will increase the amount of drug available for renal clearance. Given the time-dependent efficacy of penicillins, decreased protein binding has the potential to reduce target attainment of adequate $\%fT_{>MIC}$.

It is recognized that obese patients have a higher hepatic clearance of drugs due to increased glucuronidation and the activity of specific cytochrome P450 enzymes [31]. In particular, an increase in CYP2E1, CYP2C9, CYP2D6 and CYP2C19 enzyme activity and a reduction in CYP3A4 has been reported [18, 31]. The involvement of the cytochrome P450 enzyme system is thought to be minimal for penicillin antibiotics. Most penicillins are excreted by the kidneys as intact molecules, with only a minor degree of metabolism [26, 32]. Van Seane et al. [31] also report the potential of impairment of hepatic antimicrobial clearance due to hepatic steatosis in late obesity, which is of minimal impact in the metabolism of penicillins. Hepatic steatosis and diabetes does, however, contribute to the risks of drug induced liver injury (DILI) [33, 34]. Within the penicillin class, flucloxacillin and amoxicillin-clavulanate are the agents most commonly associated with DILI, where there are additional risks reported, including being female, being over 55 years of age and having a human leukocyte antigen (HLA)-B*5701 genotype for flucloxacillin, and HLA-A*3002 and B*1801 for amoxicillin-clavulanate [33–36].

Penicillins are primarily excreted through the kidney and are revolved largely unchanged [26]. Beta-lactamase inhibitors (clavulanate and tazobactam) are also excreted by the kidneys, but to a lesser extent, especially that of clavulanate [1]. Renal clearance is directly influenced by V, renal blood flow and glomerular filtration rate (GFR). Renal clearance can be increased because of greater kidney mass and global filtration, as demonstrated in obese kidney donors who have been shown to have significantly higher glomerular planar surface area compared to that of non-obese donors [37, 38]. Conversely, renal clearance can be decreased because of chronic kidney insufficiency due to concurrent hypertension or diabetic nephrophathy [39, 40]. In the absence of comorbid conditions, GFR can be increased by approximately 62 % in obesity [18]. Accurate measurements, however, with existing equations to estimate GFR, especially in the setting of augmented renal clearance (ARC), are limited [41–44].

Obesity increases morbidity and mortality through multiple effects, including a reduction in immune responses, leading to an increased risk of a wide range of infections, including postoperative and other nosocomial infections, as well as the development of serious complications from common infections [45]. The specific impact of obesity on clinical antibiotic treatment failure is less well established. In a historical cohort study, where 16.0 % received amoxicillin and 8.8 % received phenoxymethylpenicillin, obesity was a significant risk factor for antibiotic treatment failure, after accounting for other potential confounding variables [46]. The role of penicillin antibiotics in surgical prophylaxis, where adequate tissue concentrations of drug are critical, is also limited and the poor penetration of penicillins into adipose tissue could be of concern [47]. Gulluoglu et al. [48] demonstrated the successful administration of 1 g of intravenous ampicillin-sulbactam as a pre-operative prophylaxis for breast cancer surgery in patients with a BMI $\geq$ 25 kg/m^2, and showed a significant decreased in the rate of surgical site

infection compared to placebo (65 % reduction). In regard to the studies examining TZP administration in obesity, few studies also collected clinical outcome data. Zakrison et al. [49] reported, in a post hoc analysis, a reduced response rate in complicated intra-abdominal infections in patients with a BMI $\geq$ 30 kg/m^2 who received TZP (response rate 65 % compared with 86 % for patients with a BMI < 30 kg/m^2). More clinical outcome studies with PK/PD data are warranted.

Increasing antimicrobial resistance is a significant challenge to treating clinicians and represents a global problem. What is not known, however, is whether the obese cohort also have a greater tendency for the emergence of resistance while on therapy due to their altered PK/PD and relative immune dysfunction related to obesity (see Fig. 2.1, panel c) [9, 12, 13, 45]. One study, which examined the risk factors for postoperative mediastinitis due to methicillin-resistant *S. aureus* (MRSA), found that obesity was an independent predictor for infection with methicillin-sensitive *S. aureus*, only diabetes, female gender and age >70 years were found to be independent predictors for MRSA [50]. Despite this, adequate penicillin drug exposure, for the shortest effective duration, is paramount for suppressing the emergence of the resistant sub-population [12].

Recommendations

The dosing recommendation for penicillin antibiotics in obesity is complex and lacking clinical evidence. The PK changes of antibiotics in obesity have been likened to those seen in septic patients [31]. In the absence of controlled trials to provide clear dosing recommendations for penicillin antibiotics in obese patients, extrapolation of dosing evidence in sepsis is generally required. Fortunately, given the relative safety profile of the penicillin antibiotics, greater flexibility at upper range of the dosing schedule, or in the frequency of administration, is available.

An accurate assessment of renal function is paramount, given that there may be normal renal function, ARC, or renal insufficiency. When classified as obese, the proportion of the increased BMI that represents increased lean muscle mass, as well as adipose tissue, is important when predicting the impact on V. In the obese patient in ICU, the concurrent use of organ support, such as continuous renal replacement therapy, will further impact upon the dose required [51, 52]. Although additional supports, such as extracorporeal membrane oxygenation (ECMO), does not seem to significantly impact specifically on TZP levels [53], they could impact on more highly protein bound penicillin drugs, such as flucloxacillin, which are prone to sequestration in ECMO circuits [54]. Underlying co-morbid conditions, such as surgery, trauma, burns, and immune dysfunction for example, will further alter the PK via changes in cardiac output and fluid balance, development of ARC, and immune response to infection. Finally, the specific infecting pathogen(s), the MIC and the site of infection will impact upon the required dosing schedule.

Despite the limitations in published data and clinical evidence, the following recommendations can be made in regard to dosing penicillin antibiotics in patients with a BMI in the obese range ($\geq$30 kg/m^2).

- Dosing should be at the upper end of recommended doses, or increased frequency of dosing, such that the highest effective dose that can be safely administered with minimal side effects, especially in those obese patients with normal renal function or ARC.
- Consider using a front-loading strategy, where antibiotics are given at higher doses initially and then reduced to standard dosing, depending on culture results, organ function and response to therapy.
- Extended or continuous infusions, after an initial bolus dose, will best ensure that $fT_{>MIC}$ is maintained at greater than the minimum target of 40–60 % of the dosing interval, and can provide a means to achieve a $fT_{>MIC}$ closer to 100 % when faced with critical illness or immune system compromise.

There is insufficient evidence to provide specific weight-based dosing schedules for each penicillin antibiotic. Table 2.3 outlines general recommendations for specific common penicillin antibiotics. Future aims should be to utilize therapeutic drug monitoring of penicillin antibiotics in order to provide individualised drug dosing, using Bayesian estimation techniques and dosing software, in patients with increased BMIs with altered and difficult to predict PK/PD changes. This will facilitate adequate drug exposure and promote optimal clinical outcomes, similar to what has been proposed for dosing in critically ill patients [52, 55].

Table 2.3 Recommended dosing of common penicillin antibiotics in obesity

Antibiotic	Usual adult dose	Dosing in obesity	Comments
Narrow spectrum penicillins			
Benzylpenicillin, iv	1.2 Q6H—2.4 g Q4H	1.2–2.4 g Q4H	Consider extended infusion (12 h stability at room temperature)
Procaine penicillin, im	1.5 g	*Avoid if possible*	Risk of intra-lipomatous infection
Benzathine penicillin, im	900 mg–1.8 g[a]		
Phenoxymethylpenicillin, oral	500 mg Q12H	500 mg Q6H	Risk of poor adherence with more frequent dosing
Antistaphylococcal penicillins			
Dicloxacillin, oral	500 mg Q6H	1 g Q6H	Dicloxacillin preferred to flucloxacillin to limit the risk of drug induced liver injury

(continued)

Table 2.3 (continued)

Antibiotic	Usual adult dose	Dosing in obesity	Comments
Flucloxacillin, iv	1–2 g Q6H-Q4H	2 g Q6H-Q4H	High dose and frequent administration via a small peripheral cannula may be limited by thrombophlebitis. Consider also extended infusions (24 h stability at room temperature)
Aminopenicillins			
Amoxycillin, oral	500 mg–1 g Q12H-Q8H	1 g Q8H	Amoxycillin concentrates in the urine such that increased doses may not be necessary for urinary tract infections
Amoxycillin-clavulanate, oral	500/125 mg Q12H-Q8H; 875/125 mg Q12H	875/125 mg Q12H-Q8H; 1000/62.5 mg ER (2 tabs Q12H[b])	Less clavulanate and less diarrhoea with Q12H regimen. Amoxycillin-clavulanate (875/125 mg) can be combined with an additional amoxycillin dose
Ampicillin, iv Amoxycillin, iv	2 g Q6H-Q4H	2 g Q4H	Extended infusions limited by lack of stability at room temperature (stable only for 3 h at 30 mg/ml, stable 8 h at 10–20 mg/ml)
Antipseudomonal penicillins			
Ticarcillin-calvulanate, iv	3.1 g Q6H	3.1 g Q6H-Q4H	Consider administration by extended or continuous infusion, after an initial bolus dose (TIC stable for 48 h at room temperature; TZP stable for 24 h at room temperature and 12 h in an ambulatory pump)
Piperacillin-tazobactam, iv	3.375 g[b] Q6H; 4.5 g Q8H	3.375 g[b] q4 h; 6.75 g[b] Q8H (over 4 h); 4.5 g Q6H; 13.5–18 g (over 24 h)	

[a]Equivalent to 1.2–2.4 million units

[b]Dose/formulation not available in Australia. ER, extended release

The doses listed below are general recommendations only, based upon the maximum dosing recommendations and assume good renal function. This table serves as a guide only and the choice of agent and dose is dependent upon on the infection treated, the susceptibility of the organism and host factors. The use of prolonged infusion of beta-lactam antibiotics, either as extended infusion, defined as a discontinuous infusion of $\geq$2 h, or as continuous infusion, will maximize $fT_{>MIC}$, but should only be used following an initial loading dose, when intravenous access and drug stability is ensured [62, 63]

References

1. Penicillins and Related Drugs. Kucers' The Use of Antibiotics. 6th ed. CRC Press; 2010. p. 3.
2. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2011;52(4):e56–93.
3. Tam CS, O'Reilly M, Andresen D, Lingaratnam S, Kelly A, Burbury K, et al. Use of empiric antimicrobial therapy in neutropenic fever. Australian Consensus Guidelines 2011 Steering Committee. Intern Med J. 2011;41(1b):90–101.
4. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
5. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2012;54(12):e132–73.
6. Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. Crit Care Clin. 2011;27(1):1–18.
7. Crandon JL, Nicolau DP. Pharmacodynamic approaches to optimizing beta-lactam therapy. Crit Care Clin. 2011;27(1):77–93.
8. Mouton JW, Vinks AA. Is continuous infusion of beta-lactam antibiotics worthwhile? Efficacy and pharmacokinetic considerations. J Antimicrob Chemother. 1996;38(1):5–15.
9. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004;2(4):289–300.
10. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009;23(4):791–815, vii.
11. Abbott IJ, Roberts JA. Infusional beta-lactam antibiotics in febrile neutropenia: has the time come? Curr Opin Infect Dis. 2012;25(6):619–25.
12. Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S, MacGowan A, et al. Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resist Updates: Rev Commentaries Antimicrob Anticancer Chemother. 2011;14(2):107–17.
13. Drusano GL, Fregeau C, Liu W, Brown DL, Louie A. Impact of burden on granulocyte clearance of bacteria in a mouse thigh infection model. Antimicrob Agents Chemother. 2010;54(10):4368–72.
14. Al-Dorzi HM, Al Harbi SA, Arabi YM. Antibiotic therapy of pneumonia in the obese patient: dosing and delivery. Curr Opin Infect Dis. 2014;27(2):165–73.
15. Hayashi Y, Roberts JA, Paterson DL, Lipman J. Pharmacokinetic evaluation of piperacillin-tazobactam. Expert Opin Drug Metab Toxicol. 2010;6(8):1017–31.
16. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother. 1993;31 Suppl A:39–60.
17. Hites M, Taccone FS, Wolff F, Cotton F, Beumier M, De Backer D, et al. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother. 2013;57(2):708–15.
18. Tucker C, Lockwood A, Nguyen N. Antibiotic dosing in obesity: the search for optimum dosing strategies. Clin Obes. 2014;4(6):287–95.
19. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis: Off Publ Infect Dis Soc Am. 1997;25(1):112–8.
20. Miskowiak J, Andersen B, Nielsen VG. Absorption of oral penicillin before and after gastroplasty for morbid obesity. Pharmacology. 1985;31(2):115–20.
21. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608.

22. Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC, Austin RC. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. Cardiovasc Res Cent Bull. 1962;1:39–44.
23. Cockshott WP, Thompson GT, Howlett LJ, Seeley ET. Intramuscular or intralipomatous injections? N Engl J Med. 1982;307(6):356–8.
24. Australian Injectable Drugs Handbook. 6th ed. Collingwood, Victoria, Australia: The Society of Hospital Pharmacists of Australia; 2014.
25. Janson B, Thursky K. Dosing of antibiotics in obesity. Curr Opin Infect Dis. 2012;25(6):634–49.
26. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011;66 Suppl 2: ii25–31.
27. Kampmann JP, Klein H, Lumholtz B. Molholm Hansen JE. Ampicillin and propylthiouracil pharmacokinetics in intestinal bypass patients followed up to a year after operation. Clin Pharmacokinet. 1984;9(2):168–76.
28. Yuk J, Nightingale CH, Sweeney K, Levitz RE, Quintiliani R. Pharmacokinetics of nafcillin in obesity. J Infect Dis. 1988;157(5):1088–9.
29. Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, et al. Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother. 2013;57(12):6165–70.
30. Suh B, Craig WA, England AC, Elliott RL. Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis. 1981;143(4):609–16.
31. Van Saene HK, Silvestri L. Obesity and antibiotic dosing. Minerva Anestesiol. 2014;80 (9):980–2.
32. Cole M, Kenig MD, Hewitt VA. Metabolism of penicillins to penicilloic acids and 6-aminopenicillanic acid in man and its significance in assessing penicillin absorption. Antimicrob Agents Chemother. 1973;3(4):463–8.
33. Ghabril M, Chalasani N, Bjornsson E. Drug-induced liver injury: a clinical update. Curr Opin Gastroenterol. 2010;26(3):222–6.
34. Chalhoub WM, Sliman KD, Arumuganathan M, Lewis JH. Drug-induced liver injury: what was new in 2013? Expert Opin Drug Metab Toxicol. 2014;10(7):959–80.
35. Russmann S, Kaye JA, Jick SS, Jick H. Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. Br J Clin Pharmacol. 2005;60(1):76–82.
36. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet. 2009;41(7):816–9.
37. Rea DJ, Heimbach JK, Grande JP, Textor SC, Taler SJ, Prieto M, et al. Glomerular volume and renal histology in obese and non-obese living kidney donors. Kidney Int. 2006;70 (9):1636–41.
38. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91.
39. Decleves AE, Sharma K. Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis. Curr Opin Nephrol Hypertens. 2015;24(1):28–36.
40. Snyder S, Turner GA, Turner A. Obesity-related kidney disease. Prim Care. 2014;41(4):875–93.
41. Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. Pharmacotherapy. 2012;32(9):856–68.
42. 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.
43. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
44. Bosma RJ, Krikken JA, Homan van der Heide JJ, de Jong PE, Navis GJ. Obesity and renal hemodynamics. Contributions to nephrology. 2006;151:184-202.
45. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis. 2006;6(7):438–46.

46. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, et al. The effect of obesity on antibiotic treatment failure: a historical cohort study. Pharmacoepidemiol Drug Saf. 2013;22(9):970–6.
47. Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Limited; 2014.
48. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. Ann Surg. 2013;257(1):37–43.
49. Zakrison TL, Hille DA, Namias N. Effect of body mass index on treatment of complicated intra-abdominal infections in hospitalized adults: comparison of ertapenem with piperacillin-tazobactam. Surg Infect. 2012;13(1):38–42.
50. Dodds Ashley ES, Carroll DN, Engemann JJ, Harris AD, Fowler VG Jr, Sexton DJ, et al. Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. Clin Infect Dis: Off Publ Infect Dis Soc Am. 2004;38(11):1555–60.
51. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis: Off Publ Infect Dis Soc Am. 2014;58 (8):1072–83.
52. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
53. Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, et al. beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents. 2014.
54. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care. 2012;27(6):741 e9–18.
55. Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, et al. Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother. 2014;58(7):4094–102.
56. Newman D, Scheetz MH, Adeyemi OA, Montevecchi M, Nicolau DP, Noskin GA, et al. Serum piperacillin/tazobactam pharmacokinetics in a morbidly obese individual. Ann Pharmacother. 2007;41(10):1734–9.
57. Bulitta JB, Duffull SB, Kinzig-Schippers M, Holzgrabe U, Stephan U, Drusano GL, et al. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother. 2007;51(7):2497–507.
58. Hites M, Taccone FS, Wolff F, Maillart E, Beumier M, Surin R, et al. Broad-spectrum beta-lactams in obese non-critically ill patients. Nutr Diab. 2014;4:e119.
59. Sturm AW, Allen N, Rafferty KD, Fish DN, Toschlog E, Newell M, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy. 2014;34(1):28–35.
60. Cheatham SC, Fleming MR, Healy DP, Chung CE, Shea KM, Humphrey ML, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. Int J Antimicrob Agents. 2013;41 (1):52–6.
61. Deman H, Verhaegen J, Willems L, Spriet I. Dosing of piperacillin/tazobactam in a morbidly obese patient. J Antimicrob Chemother. 2012;67(3):782–3.
62. De Waele JJ, Lipman J, Carlier M, Roberts JA. Subtleties in practical application of prolonged infusion of beta-lactam antibiotics. Int J Antimicrob Agents. 2015. http://dx.doi.org/10.1016/j.ijantimicag.2015.01.007 (in press).
63. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. Curr Opin Crit Care. 2007;13 (5):598–606.

http://www.springer.com/978-3-319-44032-3

Drug Dosing in Obesity
Volume I: Antimicrobials
Zaidi, S.T.R.; Roberts, J.A. (Eds.)
2016, XIII, 133 p. 2 illus., Hardcover
ISBN: 978-3-319-44032-3