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# Navigating pharmacokinetic and pharmacodynamics challenges of β-lactam antibiotics in patients with low body weight: efficacy, toxicity, and dosage optimization

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**Yu-Ju Tseng, Chih-Hsun Tai, Guan-Yuan Chen, Yen-Lin Chen, Shih-Chi Ku, Tsung-Yu Pai and Chien-Chih Wu**

Correspondence to:
**Chien-Chih Wu**
Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, 7 Chung Shan South Road, Taipei 100, Taiwan

School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
**r93451011@gmail.com**

**Yu-Ju Tseng**
**Chih-Hsun Tai**
Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

**Guan-Yuan Chen**
Department and Graduate Institute of Forensic Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

Forensic and Clinical Toxicology Center, National Taiwan University Hospital, Taipei, Taiwan

**Yen-Lin Chen**
**Shih-Chi Ku**
Division of Chest Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

**Tsung-Yu Pai**
Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

***Abstract***

**Background:** Patients with low body weight (LBW) often exhibit altered pharmacokinetics (PK) in renal clearance and total body water. These changes complicate β-lactam antibiotic dosing, potentially resulting in suboptimal efficacy or increased toxicity.

**Objectives:** To evaluate the attainment of PK/pharmacodynamic (PD) targets, the prevalence of subtherapeutic and supratherapeutic concentrations, and the incidence of neurotoxicity among LBW patients treated with piperacillin/tazobactam (TZP), cefepime (FEP), and meropenem (MEM).

**Design:** A prospective observational study conducted at a tertiary hospital from January 2020 to December 2022.

**Methods:** Adult patients with a body mass index ⩽18.5 kg/m$^2$ who received TZP, FEP, or MEM were included. Trough serum concentrations were analyzed for PK/PD targets: 100% time above minimum inhibitory concentration (100% fT > MIC) and 100% time above four times MIC (100% fT > 4MIC). Neurotoxicity was assessed using standardized criteria. Statistical analyses identified factors associated with concentration variability and adverse outcomes.

**Results:** Seventy-two patients were included: 29 received TZP, 23 FEP, and 20 MEM. Achievement of the 100% fT > MIC target was comparable across all antibiotics (~70%), but 100% fT > 4 MIC attainment was significantly higher for FEP (47.8%) than for TZP (10.3%) and MEM (30%) ($p = 0.01$). Supratherapeutic concentrations were observed in 34.8% of FEP users compared to 3.4% and 5% for TZP and MEM, respectively ($p = 0.002$). Neurotoxicity occurred in 13% of FEP patients but was not reported in TZP or MEM groups ($p = 0.04$). Subtherapeutic concentrations were noted in approximately 30% of patients across all groups.

**Conclusion:** PK changes complicate β-lactam antibiotic dosing, resulting in frequent failure to achieve PK/PD targets. FEP demonstrated a particularly high risk of supratherapeutic concentrations and neurotoxicity. Therapeutic drug monitoring is crucial to optimize dosing and improve safety in this population.

## Plain language summary

### Optimizing antibiotic dosing in patients with low body weight: reducing risks of toxicity and improving treatment outcomes

Why was this study done? Patients with low body weight (LBW) often experience changes in how their bodies process medications, particularly in renal clearance and total body water. These changes can make it challenging to dose β-lactam antibiotics correctly, increasing the risk of ineffective treatment or harmful side effects. This study aimed to explore how

well these antibiotics achieve their pharmacological targets in LBW patients and to examine potential side effects, including neurotoxicity. What did the researchers do? The researchers conducted a prospective observational study at a large hospital over three years. We included adult patients with a body mass index of 18.5 kg/m$^2$ or less who were treated with the β-lactam antibiotics piperacillin/tazobactam (TZP), cefepime (FEP), or meropenem (MEM). Blood samples were analyzed to assess whether the antibiotics reached therapeutic levels, and any signs of neurotoxicity were evaluated using standardized criteria. What did the researchers find? The study included 72 patients: 29 received TZP, 23 FEP, and 20 MEM. About 70% of patients across all groups reached the primary pharmacological target (100% time above the minimum inhibitory concentration), but fewer met the stricter target of 100% time above four times the MIC, with FEP showing the highest achievement (47.8%). FEP also had the highest rate of excessively high concentrations (34.8%) and neurotoxicity (13%), compared to lower rates for TZP and MEM. Subtherapeutic levels were found in about 30% of patients in all groups. What do these findings mean? These results suggest that LBW patients frequently face challenges in achieving optimal antibiotic levels. Among the antibiotics studied, cefepime had a particularly high risk of neurotoxicity and excessive drug levels. Regular monitoring of antibiotic concentrations is essential to ensure safe and effective treatment for this vulnerable population.

***Keywords:*** β-lactam antibiotics, low body weight, pharmacokinetics/pharmacodynamics, therapeutic drug monitoring

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## Introduction

Sepsis and septic shock represent critical global healthcare concerns, affecting millions annually and resulting in mortality rates ranging from 1 in 3 to 1 in 6.[1] Early diagnosis and timely interventions, including appropriate antibiotic administration within the initial hours of sepsis onset, are crucial for improving outcomes.[2] Optimizing antibiotic dosing to achieve pharmacokinetic (PK) and pharmacodynamic (PD) targets can enhance clinical outcomes, minimize drug toxicity and drug resistance, and reduce mortality.[3] However, achieving adequate PK/PD targets for patients with extreme body weight is challenging.[4,5] In obese individuals, drug clearance may be increased due to elevated cardiac output, enhanced renal perfusion, and the activation of certain cytochrome P450 (CYP) enzymes. However, obesity can also inhibit the activity of some CYP450 enzymes, and the accumulation of fat in the liver can alter hepatic blood flow, potentially reducing drug clearance.[6] Therefore, patients with obesity face the dual risks of underexposure or overexposure to medications, depending on the dosing strategy employed and the impact of body weight on drug clearance. A systematic review of antibiotic dose adjustments in patients with obesity revealed that of the 19 drugs evaluated, 8 (42%) required dosage modifications. Among these, four drugs necessitated an increase in dosage, whereas the remaining four required dosage reduction.[7]

Despite numerous recommendations for adjusting antibiotic dosages in patients with obesity, guidelines for patients with low body weight (LBW) remain notably deficient. Similar to individuals with obesity, individuals with LBW may also exhibit the varying effects of different CYP450 enzymes, potentially leading to unpredictable drug concentrations.[8] Furthermore, research suggests a proportionate relationship between body weight and drug clearance, implying that patients with LBW may experience reduced drug clearance.[9] Currently, only a few case reports and studies have revealed

a correlation between LBW and adverse drug reactions, but serum concentrations were not explored in these studies.[10–13] β-Lactam antibiotics such as piperacillin/tazobactam (TZP), cefepime (FEP), and meropenem (MEM) are commonly employed to treat nosocomial infections, and LBW prevalence is high in Asian populations.[14] Therefore, this study investigated the proportion of patients with LBW who achieved PK/PD targets as per the currently recommended dosages and explored the incidence of excessive drug concentrations.

## Methods

### *Study population*

This prospective observational study was conducted from January 2020 to December 2022 at National Taiwan University Hospital (NTUH). The reporting of this study conforms to the STROBE statement.[15] Adult patients (age ⩾20 years) with a body mass index (BMI) of ⩽18.5 kg/m² who received TZP, FEP, or MEM were enrolled. Patients were excluded if they had acute kidney injury during antibiotic treatment or required renal replacement therapy for acute illness.[16]

A standardized case report form was used to collect data on demographic characteristics (age, sex, height, and weight), serum creatinine ($S_{Cr}$), and serum cystatin C (Cys) on the therapeutic drug monitoring (TDM) day, Charlson Comorbidity Index (CCI) scores and underlying diseases, ICU admission, and 30-day mortality. The β-lactam antibiotic dose, frequency, infusion time, duration, indication, microbiologic data, and occurrence of neurotoxicity during antibiotic use were also recorded. To be classified as having neurotoxicity, patients were required to meet two or more of the National Cancer Institute criteria for neurological toxicity.[17] These criteria include symptoms such as new-onset confusion, delirium, and drowsiness. Additionally, patients had to fulfill at least one of the following three criteria: (i) documentation of central nervous system-related neurotoxicity by a neurology consultation, (ii) improvement in neurotoxicity signs and symptoms following discontinuation of the drug, or (iii) a decrease of at least one point in the neurological component of the Sequential Organ Failure Assessment score, based on a comparison between the score recorded on the first day of β-lactam antibiotic administration and the score at the time of Glasgow Coma Scale evaluation.[18]

### *Sampling of β-lactam antibiotics and PK/PD analysis*

Empirical dose selection of β-lactam antibiotics was performed at the discretion of the treating physician or as suggested by the pharmacist, considering the severity of illness, infection site, and renal function. In our institution, the usual doses of TZP, FEP, or MEM are 4.5 g q6h, 2 g q8h, and 1 g q8h for creatinine clearance ($CL_{Cr}$) of >40, 60, or 50 mL/min, respectively. Due to the scarcity of data for patients with LBW, we employed the recommended pediatric dosages of these antibiotics to differentiate between patients receiving high and low doses. High doses were defined as those exceeding 400 mg/kg/day for TZP, 150 mg/kg/day for FEP, and 60 mg/kg/day for MEM.[19] When patients received renal dose adjustments, the administered dose was normalized to the dose they would have received if their renal function were normal before group classification.

Trough concentrations were measured within 30 min before the next scheduled dose, following the administration of at least four prior doses. This approach ensured the collection of samples in a steady-state condition.

The total serum concentrations of each antibiotic were quantitatively assessed, and the free serum concentrations were calculated by multiplying the total serum concentrations by their respective unbound fractions (TZP: 0.7, FEP: 0.8, and MEM: 0.98). The criteria of 100% of the time above the minimum inhibitory concentration (100% fT > MIC) and four times MIC (100% fT > 4MIC) were established as the optimal PK/PD targets. Given the increased virulence of *Pseudomonas aeruginosa* in nosocomial infections and the associated elevated mortality rates, the clinical breakpoint for this pathogen was selected as the target MIC.[20] The MIC thresholds for *P. aeruginosa* were determined as follows: ⩽16 μg/mL for TZP, ⩽8 μg/mL for FEP, and ⩽2 μg/mL for MEM. Free serum concentrations of beta-lactam antibiotics falling below these values were considered subtherapeutic. Conversely, free serum concentrations exceeding 150 μg/mL for TZP, 38.1 μg/mL for FEP, and 50 μg/mL for MEM were classified as supratherapeutic.[21,22]

### *β-Lactam antibiotic assay*

TZP, FEP, and MEM stock solutions were prepared separately in methanol (MeOH) at concentrations of 1000 μg/mL. The working solutions were prepared by spiking appropriate amounts of TZP, FEP, and MEM stock solutions into 50% MeOH to obtain diluted working solutions of 1000 ng/mL.

A 50-μL aliquot of plasma was diluted with 50 μL of 50% MeOH, and followed by adding 50 μL internal standard solution mixture (5 μg/mL TZP-d5, 10 μg/mL MEM-d6 and FEP-d3). Protein precipitation was carried out by adding 250 μL ACN.

The deproteinized sample was centrifuged at 15,000 rpm for 10 min. One hundred and seventy-five microliters of deionized water was added to 25 μL of supernatant prior to the LC-ESI-MS analysis.

The UHPLC-ESI-MS/MS was performed by using an Agilent 1290 UHPLC system (Santa Clara, CA, USA) coupled with a QTrap 6500 triple quadrupole linear ion trap mass spectrometer equipped with a TurboIonSpray Interface (Sciex, Framingham, MA, USA). The injection volume was 3 μL. Separation was achieved using a Kinetex™ biphenyl column (2.1 mm × 100 mm, 2.6 μm; Phenomenex, Torrance, CA, USA). The analytical column was maintained at 40°C. The mobile phase consisted of 0.1% aqueous formic acid (solvent A) and 0.1% formic acid in MeOH (solvent B). The flow rate was 0.5 mL/min. The gradient profile was as follows: 0–0.5 min, 2% B; 0.5–3.5 min, 2%–60% B; 3.5–3.51 min, 60%–70% B; 3.51–4 min, 70%–80% B; 4–4.2 min, 80%–95% B; 4.2–5 min, 95% B. The sample reservoir was maintained at 4°C. The mass spectrometer was operated in positive ionization mode with the ion spray voltage set to 5000 V, nebulizer (gas 1) pressure set to 45 psi, drying gas (gas 2) pressure set to 50 psi, and gas temperature set to 500°C. The curtain gas pressure was 30 psi. The scheduled multiple reaction monitoring (sMRM) method contained three transitions for each analyte and internal standard as follows: m/z 518 → 143*, 160, 359 for TZP and 523 → 148*, 116, 364 for TZP-d5, 481 → 396*, 324, 167 for FEP, 484.2 → 396*, 94, 167 for FEP-d3, 384 → 141*, 340, 254 for MEM, and 390→147*, 346, 68 for MEM-d6 (*, as quantification ion).

### *Impact of various renal function assessment methods on serum concentrations of β-lactam antibiotics*

β-Lactam antibiotics are primarily eliminated through the kidneys, necessitating dosage adjustments based on the patient's renal function. Our institution currently employs the Cockcroft and Gault (CG) method for the calculation of renal function, based on which the drug dosage is adjusted.[23] However, due to the reduced muscle mass and lower $S_{Cr}$ concentrations often observed in patients with lower body weight, the CG method may overestimate renal function in these individuals. Consequently, our hospital employed actual body weight and a default $S_{Cr}$ value of 0.8 to estimate renal function for dose adjustment when $S_{Cr}$ was below 0.8 (modified CG method). By using the dosage recommendations derived from the modified CG method as a reference point, we evaluated the renal function of patients by using the formulas from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) such as 2009 CKD-EPI-$S_{Cr}$, 2012 CKD-EPI-Cys, and 2021 CKD-EPI-$S_{Cr}$-Cys equations.[24,25] We then back-calculated the recommended antibiotic doses based on these renal function estimates and compared them with those obtained through the modified CG method. By multiplying the concentrations by the ratio of these comparative values, we determined potential significant differences in the proportions of subtherapeutic, therapeutic, and supratherapeutic ranges across the various methods of renal function estimation.

### *Statistical analysis*

Continuous data were assessed using the analysis of variance (ANOVA) test and are presented as means with standard deviations. Categorical data were assessed using a chi-square test or Fisher's exact test and are presented as numbers with percentages. Cohen's kappa was employed to analyze concordance. Logistic regression was used to identify the risk factors associated with concentration outcomes. A $p$ value of $\leqslant 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS 18 (SPSS Inc., Chicago, IL, USA).

## Results

A total of 72 patients were included in this study, of which, 29 received TZP, 23 received FEP, and

20 received MEM. Demographic characteristics, including age, sex, height, weight, proportion of patients with BMI ⩽ 15, $S_{Cr}$, CCI scores, and antibiotic indication, were similar across the groups (Table 1). No patients had an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m$^2$. Serum Cys levels were significantly lower in the TZP group than in the other groups. Additionally, ICU admission rates significantly varied, with the TZP group having the highest rate at 72.4% compared with the rates of 30.4% in the FEP group and 65% in the MEM group ($p = 0.007$). Moreover, the 30-day mortality rate was significantly higher in the FEP group (21.7%) than in both the TZP and MEM groups (0%; $p = 0.03$). Furthermore, neurotoxicity was observed in 13% of the patients in the FEP group, whereas no neurotoxicity was reported in the TZP and MEM groups ($p = 0.04$).

The median daily dose of antibiotics was 16 g for TZP, 4 g for FEP, and 2.6 g for MEM. A significantly higher proportion of patients in the MEM group received higher doses (65%) compared with the TZP (27.6%) and FEP (30.4%) groups ($p = 0.02$). The attainment of 100% fT > MIC was similar across the antibiotics; however, significant differences were observed in the attainment of 100% fT > 4 MIC, with the attainment being 47.8% for FEP compared with percentages of 10.3% and 30% for TZP and MEM, respectively ($p = 0.01$). The rates of supratherapeutic concentrations were markedly higher for FEP (34.8%) than for TZP (3.4%) and MEM (5%; $p = 0.002$). Subtherapeutic concentrations were observed in 38%, 26.1%, and 30% of the patients in the TZP, FEP, and MEM groups, respectively, with no significant differences among the groups ($p = 0.65$; Table 2). At lower dosages, FEP users exhibited a higher likelihood of achieving supratherapeutic serum concentrations; conversely, higher doses of MEM led to a higher likelihood of attaining adequate serum concentrations. In addition, lower dosages of TZP were sufficient to maintain optimal serum concentrations (Figure 1). Renal function ($S_{Cr}$) was associated with supratherapeutic and subtherapeutic concentrations (Supplemental Table 1).

Among the 59 patients with available Cys data on the TDM day, dosage adjustments were assessed using the 2009 CKD-EPI-$S_{Cr}$, 2012 CKD-EPI-Cys, and 2021 CKD-EPI-$S_{Cr}$-Cys equations, and the results were compared with those obtained using the CG method. The results revealed that 45.76%, 30.51%, and 42.37% of the patients, respectively, required dosage modifications. When the 2012 CKD-EPI-Cys equation was applied, only one patient required a dose reduction, whereas the remaining patients required dose increases. Notably, no significant differences were observed in achieving adequate serum drug concentrations across the various methods employed for renal function estimation. The concordance of the concentration distribution between the CG method and the other equations was substantial ($\kappa = 0.89$; Table 3).

## Discussion

The administration of appropriate drug doses to patients with extreme body weights presents numerous PK challenges. This is the first study investigating the efficacy and toxicity of TZP, FEP, and MEM administered at conventional doses to underweight adults. Our findings revealed that the PK/PD target of 100% fT > MIC was attained in only 62.1%, 73.9%, and 70% of the patients receiving TZP, FEP, and MEM, respectively. Achieving the stricter target of 100% fT > 4MIC was even more challenging. Compared to critically ill populations, the PK/PD target attainment rate for 100% fT > MIC in this study was similar (68% vs 69%).[26,27] However, for the more aggressive target of 100% fT > 4MIC, the attainment rate in this study was slightly lower than that in critically ill patients (27% vs 38%).[27] Based on existing literature on the altered PKs in underweight patients, reduced renal clearance is expected, which should theoretically result in higher target attainment rates.[9] However, in underweight patients, the increased proportion of total body water can lead to an expanded volume of distribution for hydrophilic drugs such as β-lactams, potentially resulting in lower drug concentrations.[28] Furthermore, underweight patients may still experience augmented renal clearance (ARC) due to increased systemic stress, which could further impair PK/PD target attainment rates.[29]

Regarding toxicity, we observed that patients receiving FEP had a significantly higher likelihood of exhibiting supratherapeutic concentrations compared to those receiving TZP and MEM (34.8% vs 3.4% vs 5%, $p = 0.002$). This difference may be explained by variations in the

**Table 1.** Demographic and clinical characteristics of enrolled patients.

| Baseline characteristics | Total patients (*N* = 72) | Piperacillin/tazobactam (*N* = 29) | Cefepime (*N* = 23) | Meropenem (*N* = 20) | *p* Value |
|---|---|---|---|---|---|
| Age (years) | 62.31 ± 16.43 | 62.10 ± 6.70 | 60.04 ± 17.76 | 65.02 ± 14.75 | 0.38 |
| Age >65, *n* (%) | 39 (54.2) | 14 (48.3) | 13 (56.5) | 12 (60) | 0.69 |
| Male sex, *n* (%) | 34 (47.2) | 15(51.7) | 8(34.8) | 11(55) | 0.34 |
| Height (cm) | 159.79 ± 9.69 | 160.86 ± 9.85 | 157.91 ± 9.39 | 160.40 ± 9.69 | 0.37 |
| Weight (kg) | 41.22 ± 6.51 | 41.75 ± 6.38 | 40.03 ± 6.34 | 41.80 ± 7.03 | 0.56 |
| BMI ≦ 15, *n* (%) | 16 (22.2) | 6 (20.7) | 6 (26.1) | 4 (20) | 0.86 |
| $S_{Cr}$ (mg/dL) | 0.55 ± 0.21 | 0.53 ± 0.18 | 0.61 ± 0.21 | 0.51 ± 0.25 | 0.32 |
| Cystatin C (mg/dL)[a] | 1.02 ± 0.34 | 0.90 ± 0.28 | 1.11 ± 0.46 | 1.11 ± 0.23 | 0.01 |
| eGFR (mL/min/1.73 $m^2$)[b] | 110.07 ± 28.68 | 112.00 ± 27.76 | 103.00 ± 20.51 | 115.40 ± 36.81 | 0.33 |
| $CL_{Cr}$ (mL/min)[c] | 50.96 ± 16.47 | 53.14 ± 1.88 | 48.65 ± 12.78 | 50.45 ± 16.88 | 0.22 |
| Dose/day (g) | | 16 (12, 16) | 4 (4, 5.3) | 2.6 (2, 3) | |
| High dose, *n* (%)[d] | 28 (38.9) | 8 (27.6) | 7 (30.4) | 13 (65) | 0.02* |
| Prolonged infusion[e] | 8 (11) | 2 (7) | 4 (17) | 2 (10) | 0.481 |
| Charlson Comorbidity Index | 5 (3, 6) | 5 (3, 7) | 4 (2, 6) | 5 (3, 6) | 0.21 |
| ICU admission, *n* (%) | 41 (56.9) | 21 (72.4) | 7 (30.4) | 13 (65) | 0.007* |
| Antibiotic indication,[f] *n* (%) | | | | | 0.43 |
| Bacteremia | 17 (23.6) | 4 (13.8) | 5 (21.7) | 8 (40) | |
| Pneumonia | 49 (68.1) | 23 (79.3) | 13 (56.5) | 13 (65) | |
| Intra-abdominal infection | 6 (8.3) | 4 (13.8) | 1 (4.3) | 1 (5) | |
| Urinary tract infection | 6 (8.3) | 2 (6.9) | 3 (13) | 1 (5) | |
| Neutropenic fever | 3 (4.2) | 0 | 2 (8.7) | 1 (5) | |
| Others | 4 (5.6) | 1 (3.4) | 3 (13) | | |
| 30 days mortality | 5 (6.9) | 0 | 5 (21.7) | 0 | 0.03* |
| Neurotoxicity | 3 (4.2) | 0 | 3 (13) | 0 | 0.04* |

[a]Data available for 59 participants.
[b]Determined using the 2009 CKD-EPI creatinine formula.
[c]Determined using the modified Cockcroft and Gault method (if $S_{Cr}$ is <0.8 mg/dL, a default value of 0.8 mg/dL was employed to estimate $CL_{Cr}$).
[d]>400, 150, and 60 mg/kg/day for TZP, FEP, and MEM, respectively.
[e]Infusion time ≧180 min.
[f]Patients having more than one indication.
*$p < 0.05$.
ARC, augmented renal clearance; BMI, body mass index; $CL_{Cr}$, creatinine clearance; eGFR, estimated glomerular filtration.

**Table 2.** PK/PD target attainment for β-lactam antibiotics.

| PK/PD target and serum concentration | Piperacillin/ tazobactam (29) | Cefepime (23) | Meropenem (20) | *p* Value |
|---|---|---|---|---|
| Free trough concentration | 35.89 ± 42.07 | 34.95 ± 30.50 | 8.76 ± 12.50 | 0.02* |
| 100% fT > MIC | 18 (62.1%) | 17 (73.9%) | 14 (70%) | 0.65 |
| 100% fT > 4 MIC | 3 (10.3%) | 11 (47.8%) | 6 (30%) | 0.01* |
| Supratherapeutic concentration[a] | 1 (3.4%) | 8(34.8%) | 1 (5%) | 0.002* |
| Serum concentration within therapeutic range | 17 (58.6%) | 9 (39.1%) | 13 (65%) | 0.193 |
| Subtherapeutic concentration[b] | 11 (38.0%) | 6 (26.1%) | 6 (30%) | 0.65 |

[a]Free piperacillin >150 μg/mL, free cefepime >38.1 μg/mL, free meropenem >50 μg/mL.
[b]Free piperacillin <16 μg/mL, free cefepime <8 μg/mL, free meropenem <2 μg/mL.
*$p < 0.05$.

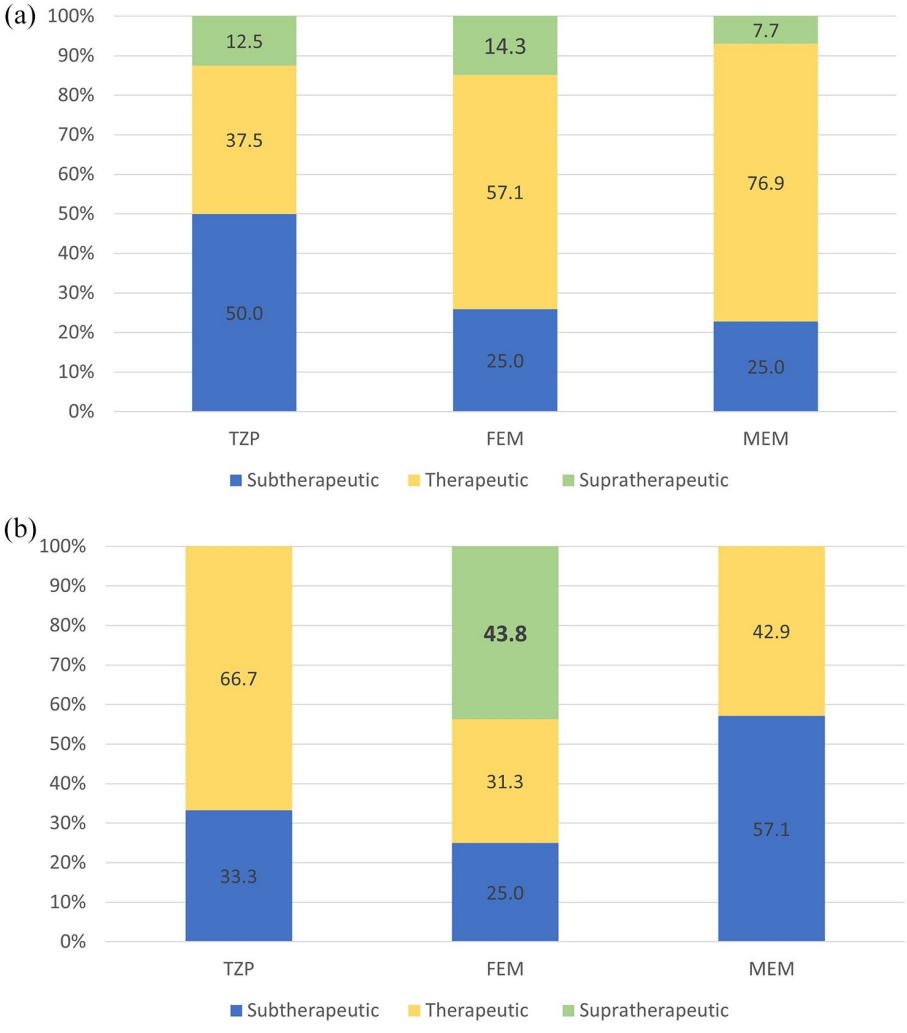


**Figure 1.** Distribution of serum concentrations in patients receiving TZP, FEP, and MEM at high or low doses: (a) high dose and (b) low dose.
FEP, cefepime; MEM, meropenem; TZP, piperacillin/tazobactam.

**Table 3.** Concordance of the CG method with other equations for concentration distribution.

| | CKDEPI-CRE 2009/CKDEPI-Cys 2012/CKDEPI-CRECys 2021* | | | |
|---|---|---|---|---|
| | | **Supratherapeutic** | **Therapeutic** | **Subtherapeutic** |
| CG | Supratherapeutic | 15 | 0 | 0 |
| | Therapeutic | 2 | 22 | 0 |
| | Subtherapeutic | 0 | 1 | 19 |

*$\kappa = 0.89$.
CG, Cockcroft and Gault.

occurrence rates of ARC, which is more common in critically ill patients. In our study population, the proportion of ICU patients was significantly higher among those receiving TZP or MEM compared to those receiving FEP (72.4% vs 65% vs 30.4%, $p = 0.007$). The higher proportion of supratherapeutic FEP concentrations may also be attributed to its relatively narrow therapeutic index compared with TZP and MEM. Some studies have adopted 150, 38.1, and 50 mg/L as the concentration thresholds for neurotoxicity of TZP, FEP, and MEM, respectively.[21,22] However, other studies have reported higher neurotoxicity thresholds for TZP and MEM (361.5 and 64.2 mg/L, respectively), suggesting greater tolerability for these two antibiotics.[30,31] In our study, all patients who experienced neurotoxicity received FEP and exhibited supratherapeutic concentrations. Given the linear relationship between drug clearance and body weight, we hypothesize that lower doses may result in a lower risk of supratherapeutic concentrations and toxicity.[9] However, in the FEP group, 43.8% of the patients in the low-dose group exhibited supratherapeutic concentrations, indicating that a lower dose may not necessarily prevent the risk of toxicity for FEP in patients with LBW. By contrast, higher doses of MEM appeared to increase the likelihood of achieving adequate serum concentration, without a significant increase in supratherapeutic concentrations. These findings are consistent with those of Luque et al., who explored the PK/PD target attainment of MEM in patients with LBW. The patients with LBW in their study received relatively high doses of MEM (median dose: 87.5 mg/kg), and 94% of patients achieved the PK/PD target of 100% fT > MIC, with only 11.1% of patients exhibiting trough concentrations of >64.2 mg/L.[32] Compared to previous studies, FEP exhibited higher average concentrations in LBW patients ($34.95 \pm 30.50$ vs $11.20 \pm 9.70$), leading to a greater proportion of supratherapeutic concentrations.[33] In contrast, the proportion of supratherapeutic concentrations for TZP (3.4% vs 13.2%) and MEM (5% vs 11.3%) was lower in LBW patients,[34] further emphasizing the differing impacts of LBW on various antibiotics.

Optimal TZP, FEP, and MEM dosing for patients with LBW remains a challenge due to the lack of specific guidance. The extremes of body size and composition can influence volume of distribution and clearance; however, the magnitude of these changes depends on the physicochemical properties of the antimicrobial (e.g., degree of ionization, molecular weight, and lipid solubility).[9,35,36] Jang et al. investigated the influence of body size on antibiotic exposure profiles, and the results revealed that patients in lower weight quartiles were more likely to achieve antibiotic PK/PD targets than those in higher weight quartiles, suggesting differences in PK parameters across various body sizes.[10] Therefore, conventional antibiotic dosing may not accurately predict serum concentrations. TDM can be valuable in guiding individual antibiotic dose, particularly in populations with unpredictable PK.[31] TDM-guided dosing for β-lactams was associated with improved clinical and microbiological outcomes and target attainment in critically ill patients.[37] Nevertheless, further research is required to support the benefits of TDM in patients with LBW. Although TDM is an ideal tool for β-lactam dosing in patients with LBW, its availability is limited to specific institutions worldwide, and the turnaround times still require improvement for its clinical application.[38,39] In our study, the PK/PD target attainment rate of 100% fT > MIC was approximately 70%. About 30% of patients had

subtherapeutic drug concentrations, with renal function being a significant influencing factor. Infected patients may experience increased physiological stress, leading to elevated cardiac output and renal perfusion, which in turn enhances drug clearance—a phenomenon known as ARC.[40] ARC further compromises target attainment rates in these patients, particularly when empirically lower doses are administered due to their LBW. Prolonged infusion of β-lactam antibiotics was associated with improved target attainment, clinical outcomes, and 90-day mortality, without an increase in adverse effects, compared with intermittent infusion in critically ill patients.[41,42] Therefore, if TDM is not available, prolonged infusion of β-lactam antibiotics may be a feasible approach in patients with LBW for enhancing target attainment rates without increasing toxicity.

Renal function estimation in patients with LBW is crucial in clinical practice, particularly when prescribing medications that are cleared through the kidneys. Creatinine-based renal function estimation methods, such as the CG method, are commonly used for the adjustment of antibiotic renal doses. However, creatinine concentrations are influenced by factors such as muscle mass, limiting their accuracy in patients with LBW.[23] Cystatin C is a small protein produced by all nucleated cells, and its concentrations are less influenced by factors such as muscle mass, making it a potentially more reliable marker for renal function estimation in patients with LBW.[43,44] For instance, CysC-based eGFR has been demonstrated to more effectively predict FEP clearance than $S_{Cr}$-based eGFR, and CysC-guided renal dosing of FEP is associated with decreased risks of encephalopathy and acute kidney injury, without increasing mortality among hospitalized patients.[45,46] Dose adjustments based on different renal function formulas may result in discrepancies in recommendations.[47] Compared with the modified CG method employed in this study, approximately 40% patients would receive higher antibiotic doses if renal function was estimated using the 2009 CKD-EPI-$S_{Cr}$, 2012 CKD-EPI-Cys, and 2021 CKD-EPI-$S_{Cr}$-Cys equations. However, these discrepancies in dose recommendations did not significantly affect the consistency of the concentration distribution. Additional research is warranted to explore the optimal renal function estimation method for dose adjustment in patients with LBW.

### *Limitations*

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the generalizability of our findings, necessitating larger studies to validate these results. Second, as a single-center study, the applicability of our findings to other settings or populations may be limited. Third, the observational design and lack of randomization may have introduced selection bias, making it difficult to establish a causal relationship between clinical outcomes. Fourth, we measured only the total concentration of β-lactams rather than the free-form concentration, which represents the active moiety, due to technical limitations. Instead, we calculated the free-form concentration using the unbound fraction of each antibiotic, as this approach provides a more accurate assessment of PK/PD targets than relying on total concentration. Although β-lactams generally have low protein binding, making their free-form concentrations relatively stable despite fluctuations in total protein levels, significant variability in protein binding has been observed for TZP, FEP, and MEM.[48] Notably, the median unbound fractions for these antibiotics were lower than those previously reported in the literature.[49] This underscores the importance of accounting for individual variability and directly measuring free drug concentrations to optimize therapy, particularly in critically ill patients. Finally, the dosage recommendations and corresponding concentration distributions based on different renal function assessment methods were estimated mathematically rather than measured directly from patient blood concentrations, which may have introduced bias. Future prospective studies should focus on evaluating the effect of various renal function assessment methods on drug dose and clinical outcomes in patients with LBW.

## Conclusion

Conventional dosing of TZP, FEP, and MEM in patients with LBW frequently results in suboptimal PK/PD target attainment, with failure to achieve adequate levels in one-third of patients. A high percentage of patients receiving FEP exhibited supratherapeutic concentrations, even in those using lower doses. Given the unpredictable serum concentrations associated with conventional dosing, TDM-guided dosing is recommended, particularly for FEP.

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Institutional Review Board (201907124RINC) of NTUH, and written informed consent was obtained from all participants or their legal representatives when participants are unconscious or unable to communicate before enrollment.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Yu-Ju Tseng:** Data curation; Formal analysis; Writing – original draft.

**Chih-Hsun Tai:** Data curation; Methodology.

**Guan-Yuan Chen:** Methodology; Validation.

**Yen-Lin Chen:** Data curation; Writing – review & editing.

**Shih-Chi Ku:** Resources; Supervision.

**Tsung-Yu Pai:** Data curation; Funding acquisition.

**Chien-Chih Wu:** Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Writing – review & editing.

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### *Competing interests*

The authors declare that there is no conflict of interest.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study can be obtained from the corresponding author on reasonable request.

## ORCID iD

Chien-Chih Wu https://orcid.org/0000-0002-9517-2176

## Supplemental material

Supplemental material for this article is available online.

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