Am J Transl Res 2026;18(2):1647-1662
www.ajtr.org /ISSN:1943-8141/AJTR0167077

Original Article

Model-guided dose optimization of cefoperazone-sulbactam and levofloxacin for pneumonia and urinary tract infections in patients with hepatic dysfunction

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Received June 27, 2025; Accepted January 14, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Objective: Dose optimization of ceftazidime-sulbactam (CFP-SUL) and levofloxacin (LVFX) for pneumonia and urinary tract infections in patients with hepatic insufficiency. Methods: A total of 100 patients were recruited from the First People's Hospital of Chun'an County and Hanchuan People's Hospital between January 2018 and November 2024. It compared two groups, with primary endpoints (successful intention-to-treat, treatment failure, 7-day clinical cure rate, time to cure, symptom improvement), secondary endpoints (reasons for treatment failure, free time (fT) > minimal inhibitory concentration (MIC) target achievement, adverse event incidence), and performed a subgroup analysis. Results: CFP-SUL's MIC values against bacterial isolates ranged from 16 to 256 mg/L, with 36.70% resistant and 63.60% susceptible. LVFX's MIC ranged from 0.25 to 64 mg/L. Compared with the standard-dose group, the model-guided group showed a significantly higher success rate (98.00% vs. 80.00%), a greater proportion of 7-day clinical cures (68.00% vs. 54.00%), a higher rate of achieving the CFP-SUL pharmacodynamic target (86.00% vs. 70.00%), and a higher rate of achieving targets for both drugs (74.00% vs. 61.00%, *P*<0.05). The incidence of treatment failures (8.00% vs. 19.00%) and adverse events (5.00% vs. 16.00%) was lower in the model-guided group (*P*<0.05). Compared with Child-Pugh Class B, Class C patients had a lower incidence of adverse reactions (3.75% vs. 15.00%, *P*<0.05) and a higher overall treatment success rate for pneumonia and urinary tract infections (92.50% vs. 82.50%, *P*<0.05). Conclusion: Model-guided CFP-SUL with LVFX dose optimization in pneumonia with urinary tract infection and hepatic dysfunction improves patient acceptance of intention-to-treat and treatment outcomes.

Keywords: Cefoperazone-sulbactam, levofloxacin, hepatic dysfunction, pneumonia, urinary tract infection

Introduction

Patients with hepatic impairment are prone to life-threatening infectious diseases due to compromised immune function and metabolic abnormalities, particularly pneumonia and urinary tract infections [1]. It has been reported that the mortality rate of patients with cirrhosis accompanied by infection increases four times [2]. Studies have also demonstrated that among critically ill patients with liver disease, the 30-day mortality rate associated with pneumonia increases by 2.95 times [3]. Additionally, the incidence rate and mortality rate of urinary tract infections in patients with hepatic impairment rise significantly, resulting in prolonged hospital stays and increased economic burdens [4]. These infections not only exacerbate the patients' condition but also profoundly impact treatment outcomes and prognosis.

The liver, as a crucial organ for metabolism and detoxification in the body, when its function is impaired, not only affects drug metabolism and clearance but may also result in drug accumulation in the body, thereby elevating the risk of adverse events [5]. Cefoperazone-sulbactam (CFP-SUL) and levofloxacin (LVFX) are widely employed broad-spectrum antibiotics in clinical practice for the treatment of various bacterial infections [6, 7]. CFP-SUL is primarily excreted via the biliary system, whereas LVFX is mainly

https://doi.org/10.62347/GIGU1376

metabolized by the kidneys [8, 9]. However, severe hepatic dysfunction can substantially alter the metabolic pathways of these two drugs. Hepatic dysfunction may diminish the biliary excretion of CFP-SUL, prolonging its half-life in the body, thereby heightening the risk of drug accumulation and toxicity reactions [10]. Additionally, the renal excretion of LVFX may also be influenced by reduced renal blood flow resulting from hepatic dysfunction, thereby further complicating the drug clearance process [11]. These changes may not only result in a reduction of the efficacy of antimicrobial therapy but also augment the risk of serious adverse events for patients, especially when used in combination. Furthermore, the complexity of treating hepatic dysfunction combined with concurrent dual infections of pneumonia and urinary tract further exacerbates the difficulty and challenges of treatment. Traditional fixed-dose antibiotic regimens often find it challenging to balance efficacy and safety, often falling short of meeting the individualized treatment needs of patients. Therefore, investigating more precise drug dosage adjustment strategies has become an imperative issue to address.

In recent years, the utilization of model-guided strategies for optimizing antibiotic therapy has witnessed substantial advancements, particularly among patients in the Intensive Care Unit (ICU). Through individualized dose adjustments, these approaches have significantly enhanced clinical cure rates and curtailed the occurrence of adverse events [12, 13]. Model-guided individualized dose optimization techniques enable the dynamic adjustment of drug dosages. This is achieved by real-time monitoring of patients' blood drug concentrations or crucial physiological parameters. By doing so, they ensure optimal therapeutic drug exposure while simultaneously minimizing the risk of toxic side effects [14]. At present, there is a dearth of systematic research on patients with hepatic dysfunction, especially those in high-risk groups who have concurrent pneumonia and urinary tract infections. In light of this situation, we have devised a prospective randomized controlled trial. The aim of this trial is to validate the practical value of pharmacokinetic/pharmacodynamic (PK/PD) models in patients with hepatic dysfunction. It also seeks to optimize antibiotic dosage adjustment strategies, elevate clinical cure rates, reduce adverse events, and ultimately improve patients' prognoses.

Methods

Research design

This single-blind, prospective, randomized controlled clinical trial was designed to explore the dose optimization of a combined antibiotic regimen consisting of cefoperazone-sulbactam [National drug approval number H20084314, Shandong Weizhi Baike Pharmaceutical Co., Ltd.] and levofloxacin [National drug approval number H20060508, produced by FUAN Pharmaceutical (GROUP) Co., Ltd.] in patients with hepatic dysfunction (Child-Pugh class B or C) who also had concurrent pneumonia and urinary tract infections. The dose optimization was guided by PK/PD modeling. A total of 100 patients were recruited from the First People's Hospital of Chun'an County and Hanchuan People's Hospital between January 2018 and November 2024. The study received formal approval from the Ethics Committee of Chun'an County First People's Hospital (Approval Number: 2025-03-09-09), and all research procedures were carried out in strict compliance with the Declaration of Helsinki. Prior to randomization, written informed consent was obtained from either all patients or their legal representatives. To safeguard patient privacy and maintain data integrity, all research data were subjected to two rounds of rigorous review.

Participants

Inclusion criteria: (1) Aged 18 years and above. (2) Diagnosed with community-acquired or hospital-acquired pneumonia complicated with urinary tract infection according to *Guidelines for the Diagnosis and Management of Community-Acquired and Hospital-Acquired Pneumonia in Adults* and Expert consensus on diagnosis and treatment of urinary tract infections [15, 16]. (3) Hepatic dysfunction (Child-Pugh B or C grade) [17]. (4) Agreed to sign an informed consent form.

Exclusion criteria: (1) History of allergy or resistance to CFP-SUL or LVFX. (2) Pregnant or lactating women. (3) Severe renal insufficiency [Glomerular Filtration Rate (GRF) <30 ml/min].

(4) Concurrent use of medications that may affect drug metabolism [such as potent cyclophosphamide (CYP) inhibitors/inducers]. (5) Participation in other clinical trials. (6) Presence of other severe complications. (7) History of drug abuse or dependence. (8) Presence of such complications as respiratory failure or sepsis.

Randomization and blinding

Patients were prospectively recruited and completed enrollment and randomization within 24 hours of hospital admission. Randomization was conducted with a computer-generated random number table with central randomization to ensure allocation concealment. Due to the personalized dose adjustments in the study, blinding was not feasible. To minimize measurement and assessment bias, an assessor-blinded approach was adopted. Specifically, the evaluation of primary and secondary endpoints was conducted by an independent committee or researchers who were unaware of the patients' group assignments. All statisticians also remained blinded to the group allocations until the final analysis was completed. During the research process, if a patient experienced severe adverse events, no longer met the inclusion criteria, or could not continue the trial due to changes in their condition, the researcher could decide to withdraw the patient from the trial based on the specific circumstances, with detailed reasons for withdrawal recorded. Patients who were lost to follow-up were considered as dropouts. All withdrawals and dropouts were documented in the Case Report Form (CRF) or Electronic Data Capture system (EDC) to minimize bias and maintain the integrity of the study results.

Grouping and model selection

Grouping: (1) Model-guided group: Following randomization, a 7-day observation period was established. For each patient, blood samples were required to be collected within 24 hours after the initial administration to evaluate the practical implementation of early dose-adjustment strategies for CFP-SUL and LVFX. Specific collection times were designated to be within the range of 15 to 30 minutes prior to the subsequent dose, in compliance with standard sampling procedures. The schedule for follow-up blood sample collection was as follows: the first follow-up blood sample was to be collected on day 3, followed by blood sample collection on day 5 and day 7. Blood samples were collected 30 minutes before and after the subsequent dose for the accurate determination of drug concentrations using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to monitor trough and peak concentrations. (A). CFP-SUL Dose Adjustment: The JPKD program software (version 3.1, website: http://pkpd.kmu.edu.tw/jpkd) served as the development platform. The User-defined Bayesian Model (UDBM) module within the JPKD software was employed for programming based on existing Population Pharmacokinetics (PPK) models to generate corresponding parameters for dose adjustment with the objective of achieving fT>MIC (the free drug time above the minimum inhibitory concentration). Dose adjustments were made based on $T_{>MIC}$ values: increase dose when $T_{>MIC}$≤90%, consider increasing dose when $T_{>MIC}$=90%-100%, maintain dose when $T_{>MIC}$=100% and steady-state minimum drug concentration <10MIC, and decrease dose when steady-state minimum drug concentration >10MIC. (B). LVFX Dose Adjustment: Dose adjustments were dynamically made based on the patient's hepatic function status to ensure area under the curve (AUC)/minimal inhibitory concentration (MIC) >100. Dosage frequency or dose was adjusted promptly to maintain blood drug concentrations within the effective range: increase dose when AUC/MIC≤113, consider increasing dose when AUC/MIC=113-125, maintain dose when AUC/MIC=125-500, and decrease dose when AUC/MIC≥500 [18].

(2) Standard-dose group: (A). CFP-SUL: Administered at a dose of 2 g/1 g via intravenous infusion every 12 hours. (B). LVFX: Given as 500 mg through intravenous infusion once a day. The duration of treatment spanned from 5 to 14 days, contingent upon the improvement in the patient's clinical symptoms. Refer to **Figure 1** for details regarding the flowchart.

Dose adjustments were performed by inputting the measured plasma drug concentrations, individual patient information, and other relevant data into the JPKD software. The software generated individualized pharmacokinetic parameters and simulated the concentration-time curve under the current dosing regimen,

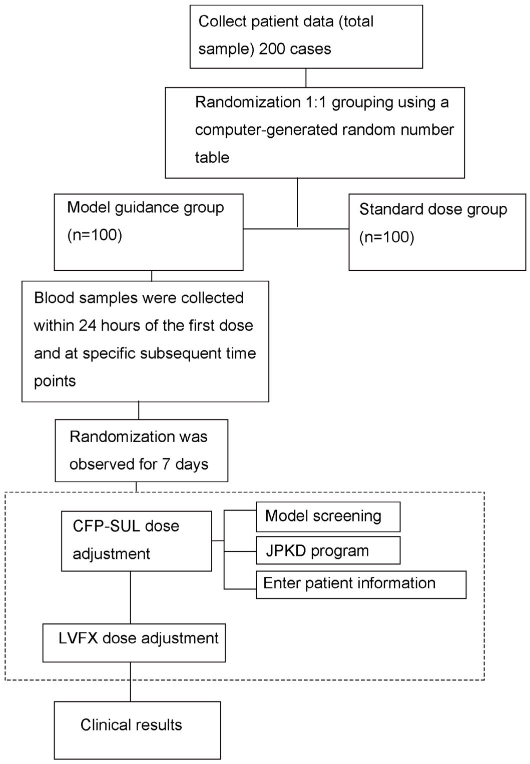

Figure 1. Research process flowchart. Note: CFP-SUL: Cefoperazone-sulbactam; LVFX: Levofloxacin.

as well as the attainment of the target PK/PD values. Based on the simulation results and predefined target goals, the JPKD software automatically calculated and provided dose adjustment recommendations. However, the software-generated dosing recommendations were not implemented automatically. Instead, they were reviewed and evaluated by an unblinded study physician.

Sample size estimation: The sample size calculation for this study was performed with "Z Tests for Two Proportions" module in PASS software (Version 2023; NCSS, LLC, Kaysville, Utah, USA) [19]. Based on relevant studies [12], assuming clinical cure rates of 90% in the model-guided group and 75% in the standard-dose group, under the conditions of a two-sided significance level of α=0.05 and a test power (1-β) of 0.80, PASS calculations determined that approximately 90 subjects were needed in each group. To account for a potential 10% dropout rate, the sample size for each group was increased to 100 subjects.

Therapeutic drug monitoring: Plasma concentrations of both agents were quantified using a fully validated HPLC-MS/MS method. Whole blood samples collected from patients were promptly centrifuged at 3,000 rpm for 10 minutes to separate plasma, which was then stored at -80°C until analysis. Prior to analysis, aliquots of plasma samples underwent protein precipitation. An internal standard working solution and a precipitating agent were added, followed by vortex mixing and high-speed centrifugation. The resulting supernatant was injected into the HPLC-MS/MS system for analysis.

Model selection: (1) Cefoperazone-sulbactam: The efficacy of this drug is related to the percentage of time the drug concentration not bound within the dosing interval exceeds the MIC (%T>MIC). For patients with severe infections, achieving a target of 100% T>MIC is recommended to ensure optimal therapeutic outcomes [18]. Based on literature reports [20], for CFP-SUL, the following model was selected for use in the JPKD as an embedded calculation model:

$$V_1 = 8.23 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta V_1}(L)$$

$$V_2 = 3.55 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta V_2}(L)$$

$$CL = 5.34 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot \left(\frac{eGFR}{90}\right)^{0.9} \cdot e^{\eta CL}(L/h)$$

$$Q = 3.54 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta Q}(L/h)$$

$$t_{1/2} = \frac{In(2) \cdot V_1}{CL}(hours)$$

$$fT_{>MIC}(\%) = \frac{\sum_{i=1}^{n} f(Cef_u^i, Sulb_u^i)}{n} \cdot 100\%$$

Where Vd is the volume of distribution (L), representing the distribution of the drug in the body; CL is the clearance rate (L/h), the rate at which the drug is cleared through metabolism and excretion; $t_{1/2}$ is the elimination half-life (h), the time required for the drug concentration to halve; eGFR is the estimated glomerular filtration rate (mL/min/1.73 m^2) with the Schwartz formula; Weight is the weight (kg); Dose is the dosage (mg); AUC is the area under the concentration-time curve (mg·h/L), used to assess drug exposure; MIC is the minimum inhibitory concentration (mg/L), the minimum effective concentration of the antibiotic against the pathogen; $e^{\eta Vd}$ is the random effect of the distribution volume; $e^{\eta CL}$ is the random effect of the clearance rate; Q is the distribution rate constant of the drug; f (Cef, Sulb) is the free drug concentration (active drug concentration not bound to proteins) measured at each sampling time.

(2) Levofloxacin: According to literature reports [21], for levofloxacin, the following model was selected for use in the JPKD as an embedded calculation model:

$$V_1 = 27.6 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta V_1} (L)$$

$$V_2 = 28.2 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta V_2} (L)$$

$$CL = (0.044 \cdot eGFR + 0.358) \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta CL} (L/h)$$

$$Q = 30.9 \cdot \left(\frac{Weight}{70}\right)^{0.75} \cdot e^{\eta Q} (L/h)$$

$$AUC = \frac{Dose}{CL}$$

$$t_{1/2} = \frac{ln(2) \cdot V_1}{CL} (hours)$$

$$f_{AUC/MIC>100}(\%) = \frac{\sum_{i=1}^{n} f(Levo_u^i)}{n} \cdot 100\%$$

General concentration prediction and dosage adjustment formulas: (1) Cefoperazone-sulbactam: a. Concentration prediction formula for multiple dosing:

$$C(t) = \frac{D}{V_1} \cdot \left(\frac{k_{21}(e^{-k_e \cdot t} - e^{-k_{12} \cdot t})}{k_{21} - k_{12}}\right) + \frac{D}{V_1} \cdot e^{-k_e \cdot t}$$

b. Dosage adjustment based on the T>MIC standard is as follows:

$$D = \frac{MIC \cdot CL \cdot T_{int}}{f_u \cdot f_{>MIC}}$$

c. At steady state, the formula for predicting blood drug concentration after multiple dosing is:

$$C_{ss,\,trough} = C_{ss,\,peak} \cdot e^{-k_e \cdot T_{int}}$$

Where C(t) is the drug concentration at time t (usually plasma concentration); D is the single dose (in mg or μg); V1 is the central compartment distribution volume; k_e is the drug elimination rate constant; k_{12} is the rate constant of transfer from the central compartment to the peripheral compartment; k_{21} is the rate constant of transfer from the peripheral compartment back to the central compartment; MIC is the minimum inhibitory concentration of the drug; CL is the drug clearance rate; T_{int} is the dosing interval; f_u is the fraction of free drug (active drug not bound to proteins); $f_{>MIC}$ is the target percentage of time the blood drug concentration is above MIC; $C_{ss,\,trough}$ is the trough concentration at steady state.

(2) Levofloxacin: a. Steady-state concentration prediction formula for single intravenous injection dosing:

$$C(t) = \frac{D}{V_1} \cdot e^{-\frac{CL}{V_1} \cdot t}$$

b. Dosage adjustment based on the AUC/MIC>100 standard is as follows:

$$Required\ Dose = AUC_{target} \times CL$$

c. At steady state, the formula for predicting blood drug concentration after multiple dosing is:

$$C_{ss,\,trough} = C_{ss,\,peak} \cdot e^{-\frac{CL}{V_1} \cdot T}$$

Where C_{peak} is the peak concentration; AUC is the area under the drug-time curve (mg·h/L), used to assess drug exposure; MIC is the minimum inhibitory concentration; AUC target is the target AUC (usually 100 times the MIC); $C_{ss,\,trough}$ is the trough concentration at steady state.

Evaluation indicators

General information of patients and other clinical pathological factors: (1) General Information: Age, gender, body mass index (BMI), smoking history, alcohol history, liver function status (categorized as Child-Pugh score B or C), presence of diabetes, chronic obstructive pulmonary disease (COPD), presence of cardiovascular disease, type of pneumonia infection (including community-acquired pneumonia, hospital-acquired pneumonia, etc.), infecting pathogens. (2) Laboratory Examination Indicators: White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (Cr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), procalcitonin (PCT), urine white blood cell count, urine red blood cell count, urine bacterial culture results. (3) Bacterial Isolate MIC Values: For all patients, bacterial isolates would be obtained and the minimum inhibitory concentration (MIC) of each isolate would be determined. If pathogens are not isolated from a patient, the MIC values most sensitive to potential pathogens for that patient would be selected based on local bacterial epidemiological information at the research center.

Main endpoints: (1) Number of Patients Successfully Receiving Intended Treatment: The total count of patients who are capable of commencing and adhering to the prescribed antibiotic treatment regimen as outlined. (2) Number of Treatment Failures: The aggregate number of patients who failed to attain the pre-established treatment objectives within the study timeframe, or who were unable to proceed with the study protocol owing to severe adverse events, premature cessation of treatment, or other factors. (3) Time from Treatment to Clinical Cure Hospitalization: The time from the initiation of antibiotic treatment (i.e., time of first dose) to when the patient meets the clinical cure criteria (i.e., complete resolution of pneumonia and urinary tract infection symptoms) in terms of hospitalization days. Clinical cure assessment criteria include: restoration of body temperature to the normal range (36.5°C-37.5°C); normalization of white blood cell count (4.00-11.00×10^9/L); absence of rales, wheezing, or other abnormal respiratory sounds upon auscultation; normal urine analysis results with no leukocytes, red blood cells, or bacterial increase; imaging studies showing complete resolution of pulmonary inflammatory lesions without any new infiltrates or nodules. Imaging recovery serves as an additional criterion, and all other indicators must be met concurrently. (4) Number of Patients with Clinical Cure within 7 Days: The count of patients who experience the complete resolution of pneumonia and urinary tract infection symptoms within 7 days following the initial antibiotic treatment. (5) Pneumonia Improvement Time: The time span needed for a significant improvement in pneumonia symptoms from the commencement of antibiotic treatment. This includes the restoration of body temperature to the normal range (36.5°C-37.3°C); the absence of rales, wheezing, or other abnormal respiratory sounds upon auscultation; and a reduction of at least 50% in the area of pulmonary inflammatory lesions. (6) Urinary Tract Infection Improvement Time: The time taken for the restoration of body temperature to the normal range (36.5°C-37.3°C), the disappearance of urinary system symptoms, and the normalization of urine analysis results with no elevation in leukocytes, red blood cells, or bacteria.

Secondary endpoints: (1) Reasons for Treatment Failure: Reasons why the predetermined treatment goals were not achieved during or after antibiotic treatment, necessitating treatment adjustment or discontinuation. All reasons for treatment failure would be categorized and recorded in the Electronic Data Capture (EDC) system. (2) Attainment Rate of free time (fT)>MIC Target: Evaluation of whether each patient achieved the fT>MIC target throughout the entire treatment period based on fT>MIC targets (such as CFP-SUL fT>MIC≥50%, LVFX fT>MIC≥30%), calculating the proportion of patients in the model-guided group and standard-dose group who simultaneously achieved the CFP-SUL and LVFX fT>MIC targets. (3) Incidence of Adverse Events: Incidence of changes in liver function indicators (such as ALT, AST, bilirubin, etc.) and other drug-related toxic reactions (such as allergic reactions, gastrointestinal reactions, etc.) throughout the entire treatment period. All adverse events would be meticulously documented in the EDC system, including event type, occurrence time, severity, and management measures.

Statistical analysis

The experimental data collected were analyzed with SPSS version 26.0. For normality testing, the Shapiro-Wilk test was employed. Among the continuous variables within the experimental dataset, those adhering to a normal distribution were characterized using the mean ± standard deviation ($\overline{x}\pm s$) (including age, BMI, clinical pathology, etc.). Continuous variables that did not conform to a normal distribution were described using the median along with quartiles [M (Q_{25}, Q_{75})] (such as time from treatment to clinical cure hospitalization). Categorical variables were presented in terms of frequency and corresponding percentages [n, (%)] (including main endpoints, etc.). A significance level of $P<0.05$ was deemed statistically significant for determining differences.

Results

General information of patients and other clinical pathological factors

A total of 200 eligible hospitalized patients were enrolled in this study. When comparing the two groups, it was found that there were no statistically significant differences in terms of general baseline characteristics, types of pneumonia infection, and predominant pathogens causing pneumonia ($P>0.05$). Among all the patients included, based on their liver function status, 120 patients were classified as having a Child-Pugh score of B, while 80 patients were classified as having a Child-Pugh score of C. The distribution of the Child-Pugh B/C ratios did not exhibit any statistically significant differences between the two groups ($P>0.05$), as detailed in **Table 1**. At the time of enrollment, the laboratory examination indicators did not show any significant differences between the two groups ($P>0.05$), as presented in **Table 2**. The results of drug sensitivity testing indicated that the Minimum Inhibitory Concentration (MIC) values of CFP-SUL against the bacterial isolates ranged from 16.00 to 256.00 mg/L. The resistance rate of CFP-SUL was 36.70%, while the sensitivity rate was 63.60%. For LVFX, the MIC range was 0.25 to 64.00 mg/L, with a resistance rate of 18.70% and a sensitivity rate of 81.30%. These findings were shown in **Table 3** and **Figure 2**.

Main endpoints

(1) Number of patients successfully receiving intended treatment: In the model-guided group, 92 patients successfully received the intended treatment, representing 92.00% of the group. In the standard-dose group, 81 patients achieved the same, accounting for 81.00% of their group. The disparity between the two groups was statistically significant ($P<0.05$). Number of Treatment Failures: The model-guided group experienced 8 cases of treatment failure, which is 8.00% of the group. In contrast, the standard-dose group had 19 treatment failures, amounting to 19.00% of the group. This difference between the two groups was statistically significant ($P<0.05$). The primary causes of treatment failure included severe adverse events, premature discontinuation of treatment, and inadequate control of the infection. Time from Treatment to Clinical Cure Hospitalization: The median hospitalization time for the model-guided group was 15.50 (7.00, 19.00) days, while for the standard-dose group, it was 15.50 (7.25, 20.00) days. There was no statistically significant difference between the two groups ($P>0.05$). Most patients demonstrated marked improvement in symptoms following antibiotic treatment and were able to attain clinical cure within the specified timeframe, which included normalizing body temperature, white blood cell count, imaging results, and urine analysis, among other indicators. Number of Clinical Cures within 7 Days: In the model-guided group, 68 patients (68.00%) achieved clinical cure within 7 days after the first dose. In the standard-dose group, 54 patients (54.00%) reached this milestone. The difference between the two groups was statistically significant ($P<0.05$). For detailed information, refer to **Table 4**.

(2) Pneumonia improvement time: There was no significant difference in the time required for significant improvement in pneumonia-related symptoms from the start of antibiotic treatment between the two groups [model-guided group mean (12.54±2.15) days vs. Standard-dose group (12.65±2.84) days, $P>0.05$]. Urinary Tract Infection Improvement Time: The time required for improvement in urinary tract infection symptoms was similar between the two groups (model-guided group mean (13.54±3.21) days vs. Standard-dose group mean (13.34±3.17) days, $P>0.05$). The majority of patients had normal urine analysis results within the specified time frame. See **Figure 3** for details.

Secondary endpoints

(1) Reasons for treatment failure: The main reasons for treatment failure in both groups includ-

Table 1. Comparison of general information for patients in model-guided group and standard-dose group

Indicator	Total	Model-Guided Group (n=100)	Standard-Dose Group (n=100)	t/χ^2 Value	*P* Value
Age (years)	200 (100.00%)	71.54±3.45	70.94±3.33	1.251	0.212
Gender				0.084	0.772
Male	122 (61.00%)	60 (60.00%)	62 (62.00%)		
Female	78 (39.00%)	40 (40.00%)	38 (38.00%)		
BMI (kg/m^2)	21.29±1.52	21.29±1.54	21.30±1.51	0.046	0.963
Smoking History				0.874	0.350
Yes	58 (29.00%)	26 (26.00%)	32 (32.00%)		
No	142 (71.00%)	74 (74.00%)	68 (68.00%)		
Alcohol-Drinking History				0.092	0.762
Yes	64 (32.00%)	33 (33.00%)	31 (31.00%)		
No	136 (68.00%)	67 (67.00%)	69 (69.00%)		
Child-Pugh Score				0.750	0.386
B Grade	120 (60.00%)	57 (57.00%)	63 (63.00%)		
C Grade	80 (40.00%)	43 (43.00%)	37 (37.00%)		
Diabetes				0.023	0.879
Yes	63 (31.50%)	32 (32.00%)	31 (31.00%)		
No	137 (68.50%)	68 (68.00%)	69 (69.00%)		
Chronic Obstructive Pulmonary Disease				0.157	0.692
Yes	30 (15.00%)	14 (14.00%)	16 (16.00%)		
No	170 (85.00%)	86 (86.00%)	84 (84.00%)		
Cardiovascular Disease				0.094	0.760
Yes	62 (31.00%)	30 (30.00%)	32 (32.00%)		
No	138 (69.00%)	70 (70.00%)	68 (68.00%)		
Pneumonia Infection Type				0.331	0.565
Community-Acquired	118 (59.00%)	57 (57.00%)	61 (61.00%)		
Hospital-Acquired	82 (41.00%)	43 (43.00%)	39 (39.00%)		
Pneumonia Pathogen				0.790	0.940
Klebsiella Pneumoniae	84 (42.00%)	41 (41.00%)	43 (43.00%)		
Streptococcus Pneumoniae	51 (25.50%)	24 (24.00%)	27 (27.00%)		
Hemophilus Influenzae	26 (13.00%)	11 (11.00%)	15 (15.00%)		
Escherichia Coli	29 (14.50%)	14 (14.00%)	15 (15.00%)		
Others	18 (9.00%)	10 (10.00%)	8 (8.00%)		

Note: BMI: Body mass index.

ed severe adverse events (0 cases in the model-guided group vs. 3 cases in the standard-dose group), premature treatment discontinuation (2 cases in the model-guided group vs. 7 cases in the standard-dose group), disease progression or the need for a change in treatment plan (6 cases in the model-guided group vs. 9 cases in the standard-dose group). There was a statistically significant difference in the distribution of reasons (*P*<0.05), and all failure reasons have been recorded in the EDC system. Attainment Rate of fT>MIC Target: Throughout the treatment process, 86 patients (86.00%) in the model-guided group and 70 patients (70.00%) in the standard-dose group achieved the fT>MIC≥50% target with CFP-SUL (*P*<0.05). The attainment rates for LVFX fT>MIC≥30% were 80.00% vs. 72.00% (*P*>0.05). The proportion of patients simultaneously achieving the CFP-SUL and LVFX fT>MIC targets had a statistically significant difference (*P*<0.05) (model-guided group 75.00% vs. standard-dose group 61.00%, *P*<0.05). Incidence of Adverse Events: The incidence of

Table 2. Comparison of other clinical pathological factors for patients in model-guided group and standard-dose group

Indicator	Total	Model-Guided Group (n=100)	Standard-Dose Group (n=100)	t/χ^2 Value	*P* Value
WBC (×10^9/L)	5.49±1.72	5.54±1.76	5.44±1.77	0.401	0.689
RBC (×10^{12}/L)	4.89±0.51	4.93±0.56	4.85±0.50	1.066	0.288
Hb (g/L)	140.66±10.64	142.00±10.54	139.50±10.57	1.675	0.096
ALT (U/L)	18.47±5.33	18.90±5.97	18.00±5.93	1.070	0.286
AST (U/L)	15.76±2.43	15.40±3.08	16.00±2.81	1.439	0.152
TBIL (μmol/L)	8.53±1.19	8.55±1.18	8.52±1.93	0.133	0.895
Cr (μmol/L)	118.23±10.02	119.87±9.20	117.98±10.20	1.376	0.170
BUN (mmol/L)	9.71±2.03	9.55±2.11	9.84±2.64	0.858	0.392
eGFR (ml/min/1.73 m^2)	49.13±7.22	48.90±7.26	49.57±10.31	0.531	0.596
CRP (mg/L)	47.49±10.31	47.66±10.61	46.97±11.21	0.447	0.655
PCT (%)	0.24±0.11	0.24±0.05	0.25±0.10	0.894	0.372
Urine White Blood Cell Count				0.142	0.707
Positive	34 (17.00%)	16 (16.00%)	18 (18.00%)		
Negative	166 (83.00%)	84 (84.00%)	82 (82.00%)		
Urine Red Blood Cell Count				0.035	0.852
Positive	35 (17.50%)	18 (18.00%)	17 (17.00)		
Negative	165 (82.50%)	82 (82.00%)	83 (83.00%)		

Note: WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; Cr: Creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; PCT: Plateletcrit.

Table 3. Results of drug sensitivity testing for all participants (mg/L)

Indicator	MIC (mg/L)			*R*/%	*S*/%
	MIC_{range}	MIC_{50}	MIC_{90}		
CFP-SUL	16-256	64	256	36.4	63.6
LVFX	0.25-64	0.25	0.5	18.7	81.3

Note: MIC: Minimum inhibitory concentration; S: Susceptibility; R: Resistance.

adverse events throughout the treatment process was 5.00% (5/100) in the model-guided group and 16.00% (16/100) in the standard-dose group, with a statistically significant difference (*P*<0.05). The most common adverse events included mild to moderate liver function abnormalities (elevated ALT, AST), gastrointestinal reactions, and rashes, all of which were reversible or controllable. Severe adverse events (SAEs) like severe allergic reactions to drugs, acute liver failure, were rare. See **Table 5** and **Figure 4** for details.

(2) Child-Pugh B/C subgroup analysis: When stratifying by liver function, there was little overall difference between Child-Pugh B and C patients in the main endpoints. However, further subgroup analysis revealed that after adjusting individualized drug doses, the incidence of adverse reactions significantly decreased in Child-Pugh C patients (3.75% vs. 15.00%, *P*< 0.05) in both the model-guided and standard-dose groups. This reduction was mainly attributed to a decrease in liver function-related events and a faster resolution of pneumonia and urinary tract infections. The number of successfully treated patients also increased accordingly (92.50% vs. 82.50%, *P*<0.05). See **Table 6** for details.

Discussion

Pneumonia complicated by a concurrent urinary tract infection represents a prevalent and intricate infectious disease in clinical settings, particularly presenting substantial treatment hurdles for patients with compromised liver function [22]. The combined administration of CFP-SUL and LVFX is a frequently employed therapeutic approach. However, hepatic dysfunction can significantly disrupt drug metabolism and clearance, resulting in drug accumulation within the body and an elevated risk of adverse reactions [23]. This, in turn, may

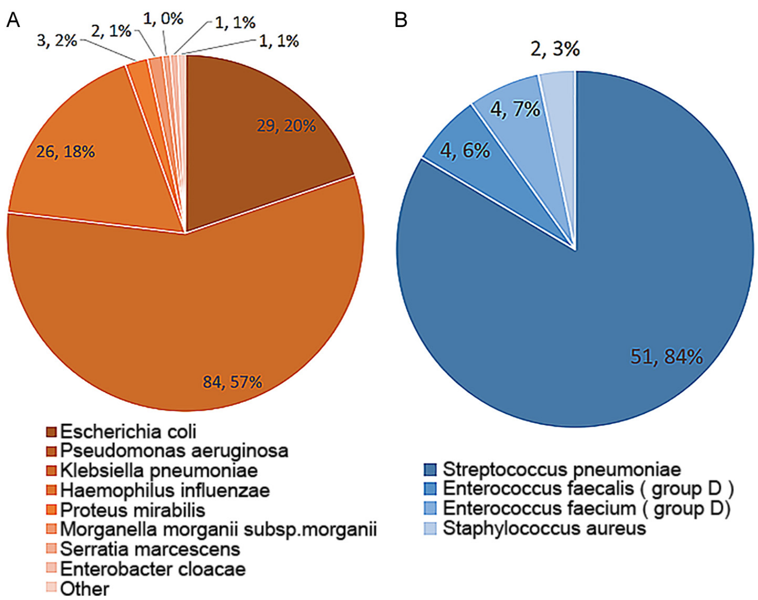

Figure 2. Urine bacterial culture results for all participants. Note: (A) represents Gram-negative bacteria, among which Pseudomonas aeruginosa accounts for the highest proportion at 57.00%, Escherichia coli accounts for 20.00%, Klebsiella pneumoniae accounts for 18.00%, and the rest accounts for less than 5.00%. (B) represents Gram-positive bacteria. Streptococcus pneumoniae accounts for the highest proportion is 84.00%, and the rest are less than 10.00%.

adversely affect the overall treatment efficacy. Consequently, investigating model-guided dose optimization strategies holds paramount clinical importance. This study revealed that, in patients with impaired liver function suffering from pneumonia and concurrent urinary tract infections, the dose optimization of CFP-SUL combined with LVFX, when guided by a model, led to enhanced patient compliance with the intended treatment regimen and superior treatment outcomes. The findings of this study demonstrate that the model-guided group outperformed the standard-dose group across several key metrics. These include the number of patients who successfully adhered to the intended treatment, the number of patients achieving clinical cure within 7 days, the attainment rate of the fT>MIC (time above the Minimum Inhibitory Concentration) target, and the incidence of adverse events. Specifically, the attainment rate in the model-guided group reached 75.00%, in contrast to 61.00% in the standard-dose group. Moreover, the adverse event rate in the model-guided group was a mere 5.00%. These disparities were found to be statistically significant when compared to the standard-dose group. Additionally, patients classified as Child-Pugh C (indicating severe liver dysfunction) exhibited lower rates of adverse events and higher rates of successful treatment under the model-guided dose regimen.

Previous studies have shown that cefoperazone is not only effective against Gram-positive aerobic bacteria but also against a variety of Gram-negative aerobic bacteria. However, its minimum inhibitory concentration is affected by the organisms that produce β-lactamase. When used in combination with sulbactam, it can overcome the effect of cefoperazone on bacteria and increase the additional coverage of anaerobic bacteria. Combined with the inherent antimicrobial activity of shu ba, both together, the sterilization effect is stronger broader [24]. In the model-guided group, precise dose adjustments are made based on individual patient characteristics (such as liver function status, drug metabolism capacity, etc.) using accurate PK/PD models. This ensures that the drug achieves more effective concentrations in the body, thereby rapidly controlling the infection and enhancing treatment efficacy [25]. This personalized dosing approach increases patient tolerance and compliance with treatment, thereby improving the likelihood of successful acceptance of intended treatment and clinical cure within 7 days [26]. In contrast, standard fixed-dose regimens do not account for individual patient differences, which can lead to some patients receiving inadequate drug doses, rendering the infection inadequately controlled, or excessive drug doses, increasing the risk of adverse reactions, thereby impacting treatment efficacy and patient willingness for treatment. Previous research by Zhang et al. [27] has also explored drug dosing optimization, with findings consistent with those of the current study, demonstrating improved treatment outcomes following dose optimization. The model-guided group, utilizing PK/PD models, can

Table 4. Comparison of treatment intention and treatment outcomes for patients in model-guided group and standard-dose group

Indicator	Total	Model-Guided Group (n=100)	Standard-Dose Group (n=100)	Z/χ^2 Value	*P* Value
Intention to Treat				16.547	<0.001
Successful	178 (89.00%)	98 (98.00%)	80 (80.00%)		
Failed	22 (11.00%)	2 (2.00%)	20 (20.00%)		
Treatment Outcome				5.181	0.023
Successful	173 (86.50%)	92 (92.00%)	81 (81.00%)		
Failed	27 (13.50%)	8 (8.00%)	19 (19.00%)		
Time from Treatment to Clinical Cure (days)	15.50 (7.00, 20.00)	15.50 (7.00, 19.00)	15.50 (7.25, 20.00)	-0.053	0.958
Clinical Cure within 7 Days				4.119	0.042
Yes	122 (61.00%)	68 (68.00%)	54 (54.00%)		
No	78 (39.00%)	32 (32.00%)	46 (46.00%)		

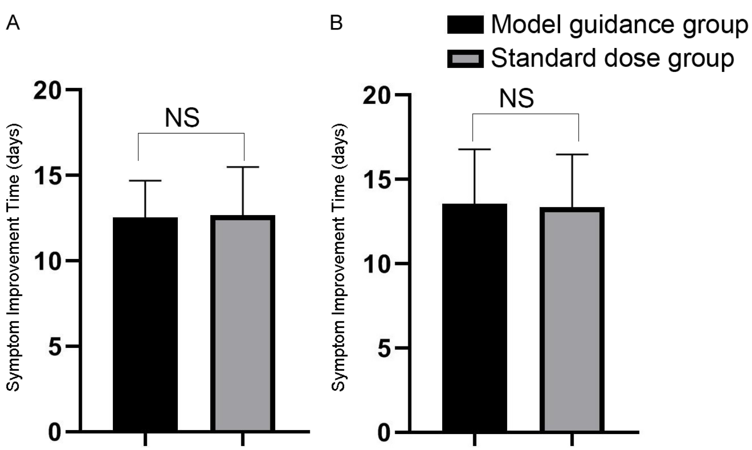

Figure 3. Comparison of improvement time for patient symptoms. Note: (A) represents pneumonia improvement time, and (B) represents urinary tract infection improvement time. NS: No significance.

more accurately predict the pharmacokinetic processes of drugs in the patient's body, adjusting drug doses to maintain drug concentrations above the MIC level for a longer duration, thus increasing the attainment rate of the fT>MIC target. Prior research by Lin et al. [28] has similarly shown that model-guided dosing improvements impact the fT>MIC target attainment rate in patients with impaired liver function, aligning closely with the findings of this study. By increasing the target attainment rate of fT>MIC, the success rate of treatment can be effectively enhanced. This might be because β-lactam antibiotics exhibit time-dependent bactericidal activity. When the time percentage of the free portion concentration (%fT>MIC) of CFP-SUL in the body remaining above MIC is relatively large, its antibacterial effect is significant. This is consistent with the research results of Tannous et al. [29]. In contrast, the standard-dose group, due to the lack of consideration for individual patient differences, may result in some patients' drug concentrations not reaching effective levels, thereby reducing the fT>MIC target attainment rate. fT>MIC is a crucial indicator affecting the efficacy of antimicrobial therapy, with a higher attainment rate of fT>MIC targets aiding in improving treatment outcomes and reducing the development of resistant bacteria [30]. Although the model-guided group optimized drug doses, there were no significant differences between the two groups in terms of time from treatment to clinical cure hospitalization, pneumonia improvement time, and urinary tract infection improvement time. This outcome may be attributed to multiple factors. On one hand, infection treatment is a complex process influenced by underlying patient conditions, infection severity, pathogen characteristics, and drug dosing [31]. Even with personalized dosing regimens, these factors can lead to variations in treatment duration among different patients [32]. Research of Chakraborty et al. [33] indicates that patients with liver dysfunction often suffer from malnutrition, weakened immune function, and compensatory changes in multiple organ functions. These factors can affect the treatment process and prognosis of patients, suggesting that the basic liver func-

Table 5. Comparison of other treatment outcomes for patients in model-guided group and standard dose group

Endpoints/Indicators	Total	Model-Guided Group (n=100)	Standard-Dose Group (n=100)	Z/χ^2 Value	*P* Value
Treatment failure	27 (13.50%)	8 (8.00%)	19 (19.00%)	7.985	0.046
SAEs	5 (18.52%)	0 (0.00%)	5 (26.32%)		
Early treatment discontinuation	8 (29.63%)	2 (25.00%)	6 (31.58%)		
Disease progression or need for a change in treatment regimen	14 (51.85%)	6 (75.00%)	8 (42.11%)		
Incidence of adverse events	22 (11.00%)	5 (5.00%)	17 (17.00%)	10.009	0.040
Mild to moderate hepatic dysfunction	6 (27.27%)	2 (40.00%)	4 (23.53%)		
Gastrointestinal reactions	5 (22.73%)	2 (40.00%)	3 (17.65%)		
Skin rash	3 (13.64%)	1 (20.00%)	2 (11.76%)		
SAEs	8 (36.36%)	0 (0.00%)	8 (47.06%)		

Note: SAEs: Serious adverse events.

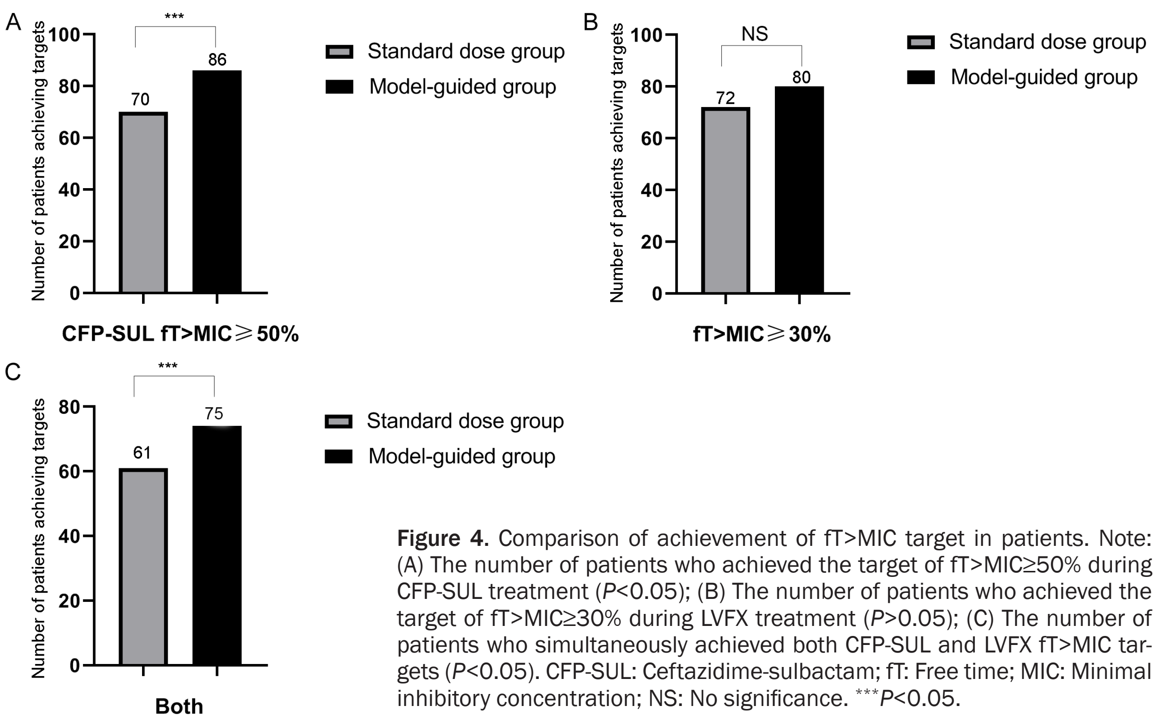

Figure 4. Comparison of achievement of fT>MIC target in patients. Note: (A) The number of patients who achieved the target of fT>MIC≥50% during CFP-SUL treatment (*P*<0.05); (B) The number of patients who achieved the target of fT>MIC≥30% during LVFX treatment (*P*>0.05); (C) The number of patients who simultaneously achieved both CFP-SUL and LVFX fT>MIC targets (*P*<0.05). CFP-SUL: Ceftazidime-sulbactam; fT: Free time; MIC: Minimal inhibitory concentration; NS: No significance. ***P<0.05.

tion status may be a key common factor influencing the treatment duration, rather than being independently changed by dose optimization. On the other hand, sample size limitations may also influence the results. A smaller sample size may fail to fully capture differences in treatment duration between the two groups.

Studies have shown that the activity of liver metabolic enzymes (such as cytochrome P450 enzyme system and glucuronosyltransferase) in patients with liver dysfunction significantly decreases, leading to an extended clearance half-life of antibacterial drugs metabolized by the liver and making them prone to adverse reactions such as drug accumulation [34, 35]. Thus, in the model-guided group, adverse events caused by drug overdose, especially those related to liver function impairment, could be avoided by precision drug dose adjustment. By optimizing drug doses, the incidence of other adverse reactions stemming from inadequate or excessive dosing is also reduced [36]. In contrast, the standard dose group fails to account for individual patient differences, potentially resulting in inappropriate drug doses for certain patients. This is particularly prob-

Table 6. Comparison of treatment outcomes in child-pugh B/C subgroups

Indicator	Total	Child-Pugh B (n=120)	Child-Pugh C (n=80)	t/Z/χ^2 Value	*P* Value
Incidence of Adverse Events	25 (12.50%)	22 (18.33%)	3 (3.75%)	10.021	0.040
Mild to Moderate Hepatic Abnormalities	8 (32.00%)	7 (31.82%)	1 (33.33%)		
Gastrointestinal Reactions	5 (20.00%)	4 (18.18%)	1 (33.33%)		
Skin Rash	5 (20.00%)	4 (18.18%)	1 (33.33%)		
SAEs	7 (28.00%)	7 (31.82%)	0 (0.00%)		
Treatment Outcome				4.110	0.043
Successful	173 (86.50%)	99 (82.50%)	74 (92.50%)		
Failed	27 (13.50%)	21 (17.50%)	6 (7.50%)		
Pneumonia Improvement Time (days)	12.64±2.29	13.54±2.21	11.13±2.34	7.379	<0.001
Urinary Tract Infection Improvement Time (days)	13.54±3.19	14.25±3.15	11.84±3.05	5.368	<0.001

Note: SAEs: Serious adverse events.

lematic for individuals with hepatic dysfunction, who exhibit lower tolerance to medications. Even minor variations in drug doses can trigger adverse reactions in these patients. Therefore, personalized dose adjustments are crucial for minimizing the incidence of adverse events [37]. Subgroup analysis revealed that patients classified as Child-Pugh B experienced a higher frequency of adverse reactions, indicative of more severe liver damage and compromised drug metabolism and tolerance. Conversely, the model-guided group, through individualized drug dose adjustments, was better able to accommodate the physiological status of patients with Child-Pugh C classification. This approach reduced drug-induced liver damage and subsequently lowered the incidence of adverse events. Moreover, appropriate drug doses facilitated more effective infection control, leading to a more rapid resolution of pneumonia and urinary tract infections, and consequently, an increase in the number of successfully treated patients [38]. In summary, this study represents a pioneering effort in optimizing drug doses using PK/PD models for patients with hepatic dysfunction suffering from dual infections, thereby addressing a significant gap in the existing literature. By comparing the effects of model-guided dosing regimens with standard fixed-dose regimens, the study unequivocally demonstrates the superiority of model-guided dosing in enhancing treatment outcomes and reducing the incidence of adverse events. The findings of this research provide a more scientific and precise treatment approach for patients with hepatic dysfunction and dual infections, ultimately contributing to improved treatment success rates and enhanced quality of life for these patients.

This study has certain limitations. Firstly, due to individualized dose adjustments, blinding of the researchers was not feasible, and only independent assessors conducted blinded assessments of endpoints. This design may introduce investigator bias, especially in subjective aspects such as dose adjustments and adverse event recording. Secondly, the sample size was relatively small, which could impact the accuracy and reliability of the study results. Moreover, the study only included patients from selected hospitals, potentially introducing selection bias, limiting the generalizability of the study results. Additionally, while the model-guided dose optimization strategy showed advantages in this study, such practical considerations as drug costs and patient compliance need to be taken into account. Future research could expand the sample size, conduct multicenter studies with larger samples to validate the effectiveness and safety of model-guided dose optimization strategies. Meanwhile, although the model has been constructed, its validity requires further evaluation, which will be a key focus of our subsequent in-depth research. Furthermore, exploring additional pharmacokinetic/pharmacodynamic indicators, optimizing models, and increasing the precision of dose adjustments could be beneficial. Additionally, studying the application effects of model-guided dose optimization strategies in patients with different pathogens and varying disease severity levels could provide more comprehensive insights for clinical treatments.

Conclusion

In conclusion, the model-guided optimization of CFP-SUL combined with LVFX in patients with hepatic dysfunction suffering from pneumonia and concurrent urinary tract infections leads to improved patient compliance with intended treatment, better treatment outcomes, and lower incidence of adverse events. This dose optimization strategy holds significant clinical value and provides a new approach and method for the treatment of patients with hepatic dysfunction facing pneumonia and urinary tract infections. However, further research and refinements are needed for practical applications to enhance treatment efficacy and safety.

Disclosure of conflict of interest

None.

Abbreviations

CFP-SUL, Cefoperazone-sulbactam; LVFX, Levofloxacin; fT, Free time; MIC, Minimal inhibitory concentration; ICU, Intensive care unit; PK/PD, Pharmacokinetic/pharmacodynamic; GRF, Glomerular Filtration Rate; CYP, Cyclophosphamide; AUC, Area Under the Curve; CRF, Case report form; EDC, Electronic data capture system; HPLC-MS/MS, High-performance liquid; chromatography-tandem mass Spectrometry; UDBM, User-defined Bayesian Model; CL, Clearance rate; BMI, Body mass index; WBC, White blood cell count; ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; Cr, Blood creatinine; BUN, Blood urea nitrogen; eGFR, Estimated glomerular filtration rate; CRP, C-reactive protein; PCT, Procalcitonin.

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