Official title: Prolonged Intravenous Infusion of β-lactam Antibiotics in Early Septic Patients (PROBES)

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Study protocol:

(1) Experimental: prolonged intravenous infusion of β-lactams Antibiotics

Administer according to the PK/PD optimized regimen with the goal of increasing T>MIC. (1) Carbapenems: Calculate the daily dose according to the creatinine clearance rate and divide it into 3 times. Each time, the dose is injected intravenously at 1/2 dose for 15 minutes, and the remaining 1/2 dose is injected at a constant rate for 3 hours. (2) Cephalosporins: calculate the allowable daily dose according to the creatinine clearance rate, inject at a uniform rate within 24 hours. (3) β-lactams and β-lactamase inhibitor compound: the daily dose is calculated according to the creatinine clearance rate and injected at a uniform rate within 24 hours.

(2) No Intervention: short-term intravenous infusion of β-lactams Antibiotics:

The daily allowable dose is calculated according to the creatinine clearance rate. The carbapenems, cephalosporins and β-lactamase inhibitor compound preparations are administered in accordance with the dosage and usage required by the instructions, and the injection is generally 30 minutes.

Timetable：

Each research center is divided into 3 research phases, and the first 4 weeks of each research phase is the wash-out period. 12 weeks is a research phase, and they are randomly assigned to the participating centers of the prolonged intravenous infusion of β-lactams Antibiotics group. All infected patients admitted after the start of the research phase are subjected to a prolonged intravenous infusion of β-lactams Antibiotics regimen; and the other centers randomly assigned to enter the short-term intravenous infusion group. The participating centers will implement a routine 30-minute infusion program for all infected patients admitted after the start of the research phase. After the 12-week study period and a 4-week wash-out period is over, the newly admitted cases will be administered according to the method of the next study period. After the 4-week wash-out period is over, it enters the second research phase. In the second research phase, each participating center automatically crosses into another program group, that is, the unit that executes the prolonged intravenous infusion of β-lactams Antibiotics program in the first phase automatically executes the conventional short-term intravenous infusion program, and vice versa. The participation period of each center is at least one year, in order to cover the difference in the incidence of different pathogenic infections in different seasons throughout the year.

Patients who had been admitted to the hospital and started taking medication before the start of this study were still taking medication according to the original schedule during the washout period and were not included in this study. The dosing regimen of all enrolled cases is based on the group of the research center on the day of enrollment, and the regimen must be strictly implemented until the end of the treatment, regardless of whether the antibiotic treatment of the case crosses the research phase. The researcher should ensure the completeness and authenticity of the research data record.

Statistical analysis plan:

(1) Statistical software: All statistical analysis is mainly conducted by SAS 9.4 and R 3.6.0.

(2)

1) Full analysis set (FAS): includes cases that have been randomly assigned to the group, have used the study medication at least once, and have follow-up records.

2) Per-Protocol set (PPS): it is a subset of the ITT data set, that is, all those who complete relevant observations according to the requirements of the plan and meet the following conditions, refer to those whose compliance is between 80% and 120%, Did not seriously violate the research plan, completed all the visits, and completed the CRF, the main evaluation indicators and most other evaluation indicators are not missing.

3) Safety set (SS): All groups who have been randomized and used study drugs at least once constitute the safety set of this study. All safety information records from the subjects will be evaluated, including adverse events, serious adverse events, and abnormal changes in safety indicators that have clinical significance.

4) The efficacy indicators were analyzed by FAS and PPS population respectively. Safety analysis adopts SS population analysis.

5) Stratified analysis: According to the subject's SOFA score (2-7 points; 8 -13 points), stratified analysis is carried out on the 28-day survival rate, and PK/PD-guided optimized antibiotic regimens are explored for pus Related effects on the prognosis of patients with toxicosis.

（3）Statistical analysis content

Statistical analysis content

1). General principles of statistical analysis

All statistical tests use two-sided tests. After P value is adjusted by FDT, Q value ≤ 0.05 will be considered as statistically significant (unless otherwise specified). The description of quantitative indicators will calculate the mean, standard deviation, median, minimum, maximum, lower quartile (Q1), upper quartile (Q3), and classification indicators to describe the number of cases and percentages of each category. The general comparison of the two groups will be analyzed by appropriate methods according to the types of indicators. The comparison of quantitative data between groups will be based on the data distribution using group t test (homogeneity of variance, normal distribution) or Wilcoxon rank sum test, classification The data uses the chi-square test or the exact probability method (if the chi-square test is not applicable), and the rank data uses the Wilcoxon rank sum test or the CMH test. Kaplan–Meier description, Log-rank test and Cox regression were used for the survival time data of the study subjects. The research results of each research center are evaluated by meta-analysis to evaluate the heterogeneity and the overall research merger effect. The potential confounding bias (treatment, service, management, etc.) of each research center is analyzed using a multi-layered mixed model.

2). Baseline and demographic characteristics

Summarize the number of enrollment and make a list of dropped cases. The size of the data set in each group, the distribution of cases in each center, the comparison of the total dropout rate, and a detailed list of the reasons for termination.

The demographic characteristics (age, sex, height, body mass index, vital signs, etc.), history of allergies, etc. of the subjects were statistically described. According to the numerical characteristics of the variables, the t-test/Wilcoxon rank sum test was used to compare the quantitative data of the two groups of subjects such as age, height, and body mass index; the chi-square test/exact probability method was used to determine the gender of the subjects, post medical history, allergy history and other categorical variables for comparison.

Analysis of dropped cases: Cases that meet the criteria for dropped cases and the subjects withdrew from the study should be included in the dropped case analysis. The total dropout rate between groups and the dropout due to adverse events were compared using the chi-square test.

3). Effectiveness analysis

(1) Baseline index: Describe the baseline of each curative effect index, refer to general statistical methods for the comparison method between groups. A stratified analysis was performed

based on the subjects' SOFA score.

(2) Main efficacy indicators: The clinical efficacy is evaluated by the survival rate in the ICU and the survival rate on the 28th day after enrollment. Simultaneous FAS analysis and PPS analysis.

(3) Secondary curative effect index

① Stratified analysis of clinical effectiveness;

②Bacterial clearance rate;

③Infection recurrence rate;

④Isolation rate of new resistant bacteria;

⑤ Infection rate of newly emerging drug-resistant bacteria;

⑥Total cost of living in ICU;

⑦Total hospitalization expenses;

⑧DDD is used for antibiotics in hospital.

For all the outcome indicators, first conduct independent evaluation in each research center in accordance with general principles. Then meta-analyze the research results of each research center. Assess the heterogeneity and the combined effect of the overall study. Finally, a multivariate stratified mixed model was used to adjust the potential bias.