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

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We hereby invite you to participate in a medical research project. This informed consent form provides you with some information to help you decide whether to participate in this research. Please read the following carefully. If you have any unclear questions and terms, you can discuss with the research doctor.
Your participation in this research is completely voluntary, and the project has been reviewed by the Research Ethics Committee of Qilu Hospital of Shandong University.
Detailed Description:
Sepsis and septic shock can lead to high morbidity and mortality. The mortality of sepsis is related to inappropriate antibiotic treatment strategy. Due to the pathophysiological characteristics of patients with sepsis, the pharmacokinetics of antibiotics have changed, and antibiotic treatment strategies applied to general mild and severe infections may not be suitable for those patients. The relevant international guidelines recommend that antibiotic treatment for patients with sepsis should base on pharmacokinetic/pharmacodynamic principles, but this recommendation is based on low-level clinical evidence.

β-lactam antibiotics, including penicillins, cephalosporins, carbapenems and so on, are the most widely used antibacterial drugs in clinical practice. The best predictive parameter of those antibiotic bactericidal activity is the time during which the free drug concentration exceeds the target microbial MIC value (fT >MIC). According to Monte Carlo approach and clinical studies, as a PK/PD target value, an effective bactericidal effect can be achieved if fT>MIC reaches more than 40%; fT>MIC reaches more than 60%-70% can achieve the maximum bactericidal effect, which can be used in the treatment of severe cases. For severe infection and prevention of bacterial resistance, fT>MIC needs to reach 90%-100%.

The results of clinical studies have proved that improper or inadequate initial empiric antibiotic treatment is an independent risk factor that affects the therapeutic effectiveness and prognosis of severe infections. Important reasons for the lower-than-expected antibiotic treatment effect in severely ill patients include at least the following two factors: (1) Changes in the pathophysiological state of severely ill patients on drug metabolism, such as capillary leakage leading to increased drug distribution volume. As well as the high excretion and low obstruction hemodynamic characteristics of sepsis, increased renal blood flow leads to high excretion of water-soluble drugs, which often reduces the effective plasma concentration of the drug; (2) ICU infection of pathogenic bacteria has increased drug resistance and increased MIC. The above factors lead to the decrease of drug fT>MIC, which affects the efficacy of antibiotics. In recent years, the optimization of PK/PD-guided time-dependent antimicrobial treatment programs have confirmed that the administration method of prolonging the infusion time or continuous infusion can maintain a good steady-state blood drug concentration, prolong fT>MIC, and improve clinical curative effect, and can reduce the amount of antibiotics.

The main problems with PK/PD-guided antimicrobial therapy are: (1) Lack of convincing large sample clinical research results; (2) It has not been confirmed which subgroup (such as the sepsis severity, drug-resistant patterns of pathogens, immunocompetence) can be benefited from this strategy; (3) It is not clear whether the method of prolonged infusion can be applied

in all kinds of β-lactam antibiotics.

This study adopts multi-center, openness, cluster randomization method to group, and eliminates the bias caused by factors such as the treatment environment in a single ward through the multi-center study; through Uniform training realizes the standardization of drug delivery methods to eliminate researchers' human bias in treatment operations and observations. At the same time, the regional randomization method sets the drug delivery method for a certain research center in a certain research phase to be determined, which eliminates the operational error and observation bias when the researcher needs to face multiple drug delivery programs at the same time. It can greatly reduce research costs and human bias, and more reliably obtain the impact of PK/PD-guided antibiotic treatment on the prognosis of patients and the impact of bacterial resistance in the entire ward.

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.

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.

Inclusion Criteria:

Patients in ICU who need to be treated with β-lactam antibiotics for clinical diagnosis of infection;
Meet the diagnostic criteria of sepsis 3.0 in the previous 24h;
At assessment of eligibility, treating doctor expects patient to need treatment in ICU beyond the next calendar day.
Exclusion Criteria:

The infection is diagnosed clinically, but the acquired pathogens are not sensitive to the study drug;
Has a history of allergies to study drugs;
Those who have a serious condition and the expected survival time is less than 72 hours.

Receipt of potential study medication for > 24 hours before randomization.
Pregnancy
Death is deemed imminent and inevitable.
Receiving palliative or supportive treatment only at the time of assessment for eligibility.
Treating doctor not committed to provision of advanced life-support, including any of mechanical ventilation, dialysis, and vasopressor administration for at least the next 48 hours.
Consent not gained for study participation and entry under a waiver-of-consent not approved by the jurisdictional human research ethics committee.

Possible side effects and dangers:
The administration method specified in this program (PK/PD-guided antibiotic program) adopts the dose specified in the instruction manual, and the continuous injection time is limited to the period of stable chemical properties of the drug. The subjects of the study are all patients who live in ICU and receive high-quality life monitoring. We believe that this research program does not present unpredictable risks to the tested patients.
The adverse reactions and side effects of the therapeutic drugs themselves belong to the potential side effects and dangers accompanying the clinical diagnosis and treatment drugs, and have nothing to do with this trial. In this study, only after the choice of medication, the infusion time or infusion speed was optimized and improved. Therefore, in addition to the adverse reactions and side effects of the treatment medication itself, this research program does not have unpredictable risks for the tested patients.

Rights and responsibilities:
Personal rights and interests will be protected by the following conditions:
If the execution is based on the harm caused by the research plan, the research client will be liable for damages in accordance with the law.
1. The executing agency of this clinical research plan (the drugs of this research plan have been marketed in my country) will safeguard your rights and interests during the research process.
2. Privacy protection
(1) Research doctors and staff will keep your medical records confidential. The collected data, examination results and doctor's diagnosis will be kept confidential, and there will be a code to protect your name from being disclosed. In addition to investigations by relevant agencies in accordance with the law, we will maintain your privacy.
(2) Research data can be published for academic needs, but your privacy (such as name, medical record number... etc.) will not be published and will be kept strictly confidential.
3. You can learn about the information and research progress related to this research at any time. If you suffer any harm or have any questions about your rights during the research period, please contact Wang Hao. His contact number is 18560081013.
You do not need to give any reason, you have the right to refuse to participate in the study, and you can withdraw your consent to withdraw from the experiment at any time, and this decision will not cause any unpleasantness or affect the medical care of your doctor in the future.