Official title: mNGS -Guided Antimicrobial Treatment Versus Conventional Antimicrobial Treatment in Early Sever Community-Acquired Pneumonia among Immunocompromised Patients (MATESHIP)

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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:

Severe Community-acquired pneumonia (SCAP) is a leading global infectious cause of intensive care unit (ICU) admission (approximately 20%-30%), and the primary reason of mortality and morbidity in immunocompromised patients. There is a global increase of patients with distinct immunocompromised conditions due to the advance of cancer treatment, increasing biologics, and immunosuppressants for autoimmune diseases and growing organ transplant recipients, and it has been estimated that patients with immunocompromised conditions account for approximately 35% of all intensive care unit (ICU) admissions. Immunocompromised patients, who always at risk for mixed and unusual pathogens, have more factors to complicate with sepsis, respiratory failure, acute respiratory distress syndrome, and the mortality rate can be up to 50%. Moreover, the outcomes in immunocompromised patients with SCAP not only related to disease severity but also related to delays initiation of receiving appropriate therapy. 2019American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) community-acquired pneumonia (CAP) guideline recommends that administering appropriate antimicrobials as soon as possible is the most effective measure to improve clinical prognosis and reduce mortality rate for SCAP patients. Therefore, timely identification of pathogenic microorganisms is particularly crucial for antimicrobial treatment in immunocompromised patients with SCAP.

Conventional microbiology diagnostic methods, such as standard microbiologic cultures, microscopy, polymerase chain reaction (PCR), respiratory virus multiplex PCR, as well as pathogen-specific antigens and antibody assays, are associated with relevant limitations: (1) long culture cycle and low positive rate; (2) usually only one pathogen can be detected at a time; (3) inability to detect fastidious or difficult culture organisms; (4) pathogen antibody-based testing may be unreliable in immunocompromised patients who are unable to mount antibody responses. Conventional diagnostic methods make big challenge for pathogens diagnosis of SCAP among immunocomprised patients due to above limitations and the complicated causative microorganisms. However, conventional antimicrobial therapy based on the results of conventional microbiology diagnostic techniques, which may delay timely accurate antimicrobial therapy at the initial stage, and the mortality of immunocomprised patients with SCAP may be increased. Metagenomic next-generation sequencing (mNGS), which can quickly (usually within 24h) detect a wide array of bacteria, viruses and fungi in an unbiased manner at the same time by analyzing cell-free deoxyribonucleic acid (DNA) fragments of pathogens using appropriate lower respiratory tract specimen (LRS), is increasingly used in severe infectious disease, especially among immunocompromised patients. This study speculates that mNGS (using LRS) can guide early and accurate antimicrobial treatment for immunocomprised patients with SCAP. This multi-center, opening, randomized, controlled trail study will enroll SCAP patients with immunocompromised conditions to determine whether mNGS-guided antimicrobial treatment improve the clinical prognosis and increase the clinical cure rate. The purpose of this study is to characterize the effect of mNGS-guided antimicrobial treatment for SCAP versus conventional treatment among

immunocomprised patients. It is postulated the severity score and the consumption of antimicrobial agents will be decreased, the cure rate will be increased and the time to initiate appropriate therapy will be advanced.

Experimental: mNGS-guided treatment group
In mNGS-guided treatment group, participants undergo mNGS, using appropriate lower respiratory tract (LRT) specimens, and conventional microbiological tests (CMT). LRT specimens including endotracheal aspiration (ETA), bronchoalveolar lavage fluid (BALF) and protected specimen brush (PSB) will be obtained within 24 hours after the participants entering the ICU. CMT will be also applied using appropriate LRT specimens and other necessary specimens (such as blood, pleural fluid, urine, et al.). Clinicians alter or confirm targeted treatment of participants based on results of mNGS and CMT.
No Intervention: Conventional treatment group
In conventional treatment group, participants undergo CMT using appropriate lower respiratory tract (LRT) specimens, and other necessary specimens (such as blood, pleural fluid, urine, et al.). LRT specimens including endotracheal aspiration (ETA), bronchoalveolar lavage fluid (BALF) and protected specimen brush (PSB) will be obtained within 24 hours after the participants entering the ICU. Based on results of CMT, clinicians alter or confirm definitive treatment of participants.

Inclusion Criteria:
1.Meet the diagnostic criteria of sever community acquired pneumonia (SCAP); SCAP was defined in patients with either one major criterion or at least three minor criteria of the IDSA/ATS CAP severity criteria. Major criteria: Septic shock with need for vasopressors; Respiratory failure requiring mechanical ventilation; Minor criteria: Respiratory rate > 30 breaths/min; PaO_2/FiO_2 ratio < 250; Multilobar infiltrates; Confusion/disorientation; Uremia (blood urea nitrogen level > 20 mg/dl); Leukopenia (white blood cell count <4,000 cells/μl); Thrombocytopenia (platelet count <100,000/μl); Hypothermia (core temperature<36°C); Hypotension requiring aggressive fluid resuscitation. 2. Admission in ICU; 3. Time from SCAP diagnosis to ICU admission<24 h; 4. Patients with Immunocompromised conditions. Immunocompromised conditions were defined as: use of long-term (>3 months) or high-dose (>0.5 mg/kg/d) steroids, use of other immunosuppressant drugs, solid organ transplantation, solid tumor requiring chemotherapy in the last 5 years, hematologic malignancy regardless of time since diagnosis and received treatments, primary immune deficiency, HIV infection with a CD4 T-lymphocyte count <200 cells/ml or percentage <14%, laboratory tests show absolute neutrophil count < 1,000 cells/μl on ICU admission, or the other immunosuppression status judged by the physicians.
Exclusion Criteria:
1.Age<18 years old; 2. Pregnant or lactating women; 3. Patients with an irreversible contraindication for bronchoscopy; 4. Survival time<72 h; 5. Those who have serious underling disease and expected to die within a short period time; 6. Receiving palliative therapy or supportive treatment only.

Possible side effects and dangers:
The antimicrobial treatment procedure specified in this program (mNGS-guided antimicrobial treatment program) adopts a new therapy procedure based on results of mNGS microorganism

detection technology combined with conventional diagnosis technology. The subjects of this 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 the microorganism detection technology and the appropriate definitive antimicrobial treatment were 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.