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

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Study protocol:

Participants in this study will be randomly allocated to receive mNGS-guided treatment based on both results of mNGS and conventional microbiologial tests (CMT) (the experimental arm); or conventional treatment only based on the results of CMT (the control arm).

NO intervention arm: Conventional treatment group

In the conventional treatment group, clinicians will alter or confirm definitive treatment based on the results of CMT. Participants will undergo CMT using appropriate LRT specimens and other necessary specimens (such as blood, pleural fluid, urine, et al.). LRT specimens including endotracheal aspiration, bronchoalveolar lavage fluid (BALF), and protected specimen brush, will be obtained within 24 h of participants entering the ICU. Blood samples, mid-stream urine, pleural fluid, and other respiratory specimens will be collected as soon as possible after admission and, preferably, before antimicrobial therapy begins. CMT, including bacterial/fungal stains and cultures, single or multiple RT-PCR, blood culture, serum and urine pathogen-specific antigen tests, and serum pathogen-specific antibody tests, will be performed according to the consensus statement regarding the management of immunocompromised patients with CAP and participant conditions.

Experimental arm: mNGS- guided treatment group

In the mNGS-guided treatment group, clinicians will alter or confirm definitive treatment based on both mNGS and CMT results. Participants will undergo mNGS test using appropriate LRT specimens. CMT will also be carried out using appropriate LRT specimens and other necessary specimens (such as blood, pleural fluid, urine, et al.), as described for the control group. LRT specimens will be divided into aliquots and used for both mNGS tests and CMT.

Microbiological tests

Conventional routine microbiological tests will be performed in local laboratories. LRT samples for mNGS tests will be transferred to the same professional genomic laboratory independently by cold-chain transportation; the genomic laboratory will perform nucleic acid extraction, library construction, amplification and sequencing, bioinformatic analysis, and data interpretation. During our study period, the professional genomic laboratory will use the consistent mNGS detection protocol among the samples of enrolled patients. An independent multidisciplinary panel of senior experts, including one infectious disease specialist, an intensivist, and a microbiologist, independently adjudicate the causative microorganisms for each patient after reviewing the mNGS results and necessary clinical data.

Participants management

During hospitalization, participants will receive personalized therapy according to 2019ATS/IDSA CAP guidelines, Pneumonia Severity Index (PSI) score, and participants' conditions. Once participants combine with sepsis or septic shock, they will be managed according to International Guidelines for Management of Sepsis and Septic Shock 2021.

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 and have follow-up records. Cases missing main evaluation indicators or lost to follow-up will be excluded from FAS.

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 at least one diagnosis method 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 center, stratified analysis is carried out on the 28-day mortality rate, and mNGS-guided treatment are explored for related effects on the prognosis of patients with severe community-acquired pneumonia.

（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, The classification 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 chis-quare 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

center.

(2) Main efficacy indicators: The relative change in SOFA score from randomization to day 5, day 7, day 10, or the day of ICU discharge/death; and the consumption of antimicrobial agents during ICU stay (expressed as defined daily doses). Simultaneous FAS analysis and PPS analysis.

(3) Secondary curative effect index

①days from randomization to initiation of definitive antimicrobial treatment

②overall antimicrobial agent use and cost;

③total cost of hospitalization;

④length of ICU stay;

⑤28- and 90-day mortality; and clinical cure rate.

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.