The Protocol of

Multi-center Clinical Trial of Lactate Clearance Guided Fluid Resuscitation in Patients With Sepsis

Sponsor:	Nanfang Hospital of Southern Medical University
Central Contact Person:	Chen Zhongqing, Ph.D
Telephone:	+86 20 6164 1886
Email:	13503049103@163.com
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Brief Summary
Serum lactate level is depended on the balance between lactate production and clearance. It is seen as a sensitive indicator reflecting not only the low systemic perfusion but microcirculatory dysfunction which cause global or regional tissue hypoxia (as a result of impaired mitochondrial oxidation). 2016 Surviving Sepsis Campaign guideline stated “We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion”, with weak recommendation and low quality of evidence. Several trials which evaluated the resuscitation strategy included lactate clearance as a target while based on 2.0 diagnostic criteria for sepsis, finally showed conflicting results. The aim of this study is to explore the feasibility of lactate clearance guide resuscitation in sepsis that defined by The Third International Consensus Definitions for Sepsis and Septic shock through multi-center, central-randomization clinical trial.

Background
Sepsis is a major public health concern which affects millions of people annually and has a 28-day mortality rate of 14 to 50% depending on the patient population and the study selection criteria. The exploration and discussion of sepsis has never stopped, and it remains a great challenge for clinicians. In The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The organ dysfunction was placed in a vital position instead of SIRS, and sepsis shock was quantified by hypotension, need for vasopressor, and increased serum lactate. All of these indicators indicate that sepsis-induced hypoperfusion exist. Early effective fluid resuscitation is of critical importance to improve sepsis-induced tissue hypoperfusion or septic shock.
Rivers et al proposed an explicit protocol in 2001 which targeted four goals: a central venous pressure of 8 mm Hg or higher, the mean arterial pressure of 65 mm Hg or higher, urinary output more than 0.5 ml/kg/h, and the central venous oxygen saturation(ScvO2) was 70 percent or higher, called early goal-directed therapy (EGDT). It showed significant benefits with respect to outcome in patients with severe sepsis and septic shock. After that, EGDT was gradually accepted and used as a conventional treatment for septic patients. The Surviving Sepsis Campaign (SSC) has recommended EGDT since 2002 as the key strategy. However, three multicenter, randomized trials, ProCESS, ARISE, ProMISe, demonstrated that the addition of continuous ScvO2 monitoring and strict protocolization did not make EGDT better than usual care. Reassess these four goals in EGDT protocol, we can tell that ScvO2 is the only indicator that reflects tissue oxygen metabolism. However, there are studies confirmed that ScvO2 oriented EGDT cannot reduce the mortality of sepsis. So it is important to find out a more effective indicator. Lactate is a product of anaerobic metabolism of the body, lactate clearance has been found to effectively predict the prognosis of sepsis. Few studies have shown that lactate clearance oriented fluid resuscitation can be of benefit in patients with sepsis. Nevertheless, whether lactate clearance could be combined with sepsis Bundle as a new marker to improve

the prognosis remains a problem. The objective of this study is to discuss the feasibility of lactate clearance oriented sepsis treatment through multi-center clinical trial.

Key words
Sepsis, lactate clearance, protocolized resuscitation

Aim
The objective is to compare the prognosis of setting different goals during resuscitation of patients suffering from sepsis with hyperlactacidemia (Lac≥ 3mmol/L):(1)lactate clearance (Lac%)≥10%;(2) lactate clearance (Lac%)≥20%;(3) central venous oxygen saturation (ScvO2) ≥70%, the Early goal-directed therapy (EGDT) came up by Rivers et al in 2001 and recommended in international guidelines for the resuscitation of patients presenting with sepsis.

Methods/design
This trial is a prospective, multicenter, single-blind, parallel-group, central-randomized, controlled trial in patients with sepsis and hyperlactacidemia Patients will be stratified by center, age, initial level of lactate, and the presence/absence of neurological diseases. Each participating unit department will go through an educational program regarding study monitoring methods and study reporting methods (including goal assessments and treatment attempts).
The recruitment begins after approval from local ethics committees.

Ethics committee approvals submission/approval
Medical Ethics Committee of Nanfang Hospital 5 June 2017

Hypothesis
We hypothesized that targeting the lactate clearance (Lac%) during the resuscitation of patients suffering from sepsis will result in better prognosis as compared with those patients who set central venous oxygen saturation ($ScvO_2$) as goal.

Diagnostic criteria
1. Confirmed or suspected infection.
2. QuickSOFA (qSOFA: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less) ≥2. (Have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.)
3. The increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more
4. Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater

than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

Inclusion criteria

1. Older than 17 years old.
2. Primary diagnosis is sepsis, means being confirmed or suspected infection while have at least 2 points of qSOFA.
3. Be transferred to intensive care unit (ICU) for the first time during this hospitalization.
4. Elevated lactate ≥3.0mmol/L.

Exclusion criteria

1. Acute hemorrhage uncontrolled.
2. Known to be pregnant.
3. Known liver disease – Child-Pugh classes C, acute hepatic failure, severe hepatopathy accompany with prominent portal hypertension.
4. Known being in an immunosuppressive state:
    1) Suffering from any disease that is unrelated with sepsis that severely inhibits the immune to infection, such as: active hematological or lymphoma malignancy, or during immunosuppressive therapy, such as chemotherapy or radiotherapy.
    2) Known human immunodeficiency virus (HIV) serology positive.
5. Known chronic kidney disease.
6. Suffering from any disease that affects lactate kinetics, such as mitochondrial encephalopathy, congenital hyperlipidemia, Wernicke encephalopathy, etc. Or other probable cause of hyperlactatemia.
7. Took any drugs that affect lactate kinetics within the effective time window, such as taking metformin or phenylephrine within 1 week.
8. Suffering from any disease that restricts resuscitation, such as heart failure, cardiac surgery, severe heart disease etc, or suffered from a cardio-pulmonary resuscitation.

Participant withdrawal

Patients who meet any of the situation below are withdrawal from the protocol, meanwhile the clinician should analyze and record expatiation.

1. Fail to obtain informed consent within 2 hours.
2. Surgery or RRT (renal replacement therapy) might be required within 6 hours.
3. Patients or their kin claim to withdraw from the protocol.
4. The investigator or sponsor claim that the patients should withdraw from the protocol because of a proper therapy should be used or the patients cannot follow the protocol strictly.
5. Severe adverse reactions (SARs) that need to stop or change the interventions of protocol.
6. Loss to follow up.

Randomization

Randomization will be done by an independent team of statisticians using a computer-based algorithm to realize central-randomized. It allow immediate and concealed allocation to the intervention arm. The patient will be stratified according to the age, base-line of lactate, place that patient transferred from, and presence/absence of central nervous system disease (with obtainable medical record). Each patient will be allocated a unique patient ID-number. Randomization should be performed within 2 hours after fulfillment of the inclusion criteria in the ICU.

Primary outcome measure

All-cause mortality at 28 days.

Secondary outcome measures

All-cause mortality at 90 days.
Length of stay in the intensive care unit (ICU)
Length of stay in hospital.
All-cause mortality at 90 days.
All-cause mortality during hospitalization.
All-cause mortality during ICU stay.
Administered treatments included: crystalloid volume, vasopressor administered, dobutamine, RBC transfusion, mechanical ventilation, renal-replacement therapy.
Sequential Organ Failure Assessment (SOFA) at 24 hours.
Proportion of patients reporting treatment-emergent adverse events.

Blinding

This study follows the single-blind principle that patients do not know their own allocation. The clinicians which should be in charge of patient's administration will be aware of the allocation during the intervention period. The clinicians should be only aware of the patients' base-line of lactate in control group, while patients' base-line of ScvO2 should be available in lactate groups. After achieve the targets, patients will be handed over to other clinician who is unaware of the patients' allocation and continuing subsequent therapy.
Information on the primary outcome and other secondary outcomes will be provided by the local investigators from patient charts, but the statistician doing the analyses will be blinded to the allocation of patient.

Trial interventions

Once subjects are enrolled in the ICU, start systematic treatment of sepsis immediately following Surviving Sepsis Campaign: International Guidelines for Management International Guidelines for Management of sepsis and septic shock: 2016. The time point of taking blood sample is regarded as the beginning of research (0h). MAP, CVP, urine output, ScvO2 and blood lactate (Lac) should be assessed every 1 hour during 0 to 6h. Lactate clearance (Lac%) is defined as the percentage of lactate reduction within every two hours. So we can get a Lac% per hour starting from

2h to the end of resuscitation.

Within first two hours, fluid should be administered to achieve the same goals from EGDT in all subjects, which is still widely used in ICU, include MAP ⩾ 65mmHg, CVP 8-12mmHg, Urine output ⩾ 0.5ml/kg/h, ScvO2 ⩾ 10%. Because that the treatment of sepsis is time-dependent and many patients might be unconscious when they enrolled in the ICU, the informed consent is allowed to be done within 2 hours. Central- randomization should be done within 2 hours too, otherwise the subjects considered to be withdrawn.

Starting from the third hour, all subjects will be treated according to the targets (Appendix 1) of the allocated arm:

1. Intervention group – targeted lactate clearance (Lac%) care within 2 hours.
2. Control group – targeted central venous oxygen saturation (ScvO2) (EGDT) standard care.

Appendix 1

The trial targets for the treatment arms.

	Intervention group – targeted lactate clearance care		Control group – targeted central venous oxygen saturation care
	Lac%≥10% Group	Lac%≥20% Group	ScvO2 Group
①	MAP≥65mmHg	MAP≥65mmHg	MAP≥65mmHg
*②	CVP 8-12mmHg	CVP 8-12mmHg	CVP 8-12mmHg
③	Urine output≥0.5ml/kg/h	Urine output≥0.5ml/kg/h	Urine output≥0.5ml/kg/h
④	Lac%≥10%	Lac%≥20%	**ScvO2≥10%

*Central venous pressure (CVP) 12–15 mmHg in mechanically ventilated patients.

** Scv_{O_2} was measured by blood-gas analysis (BGA).

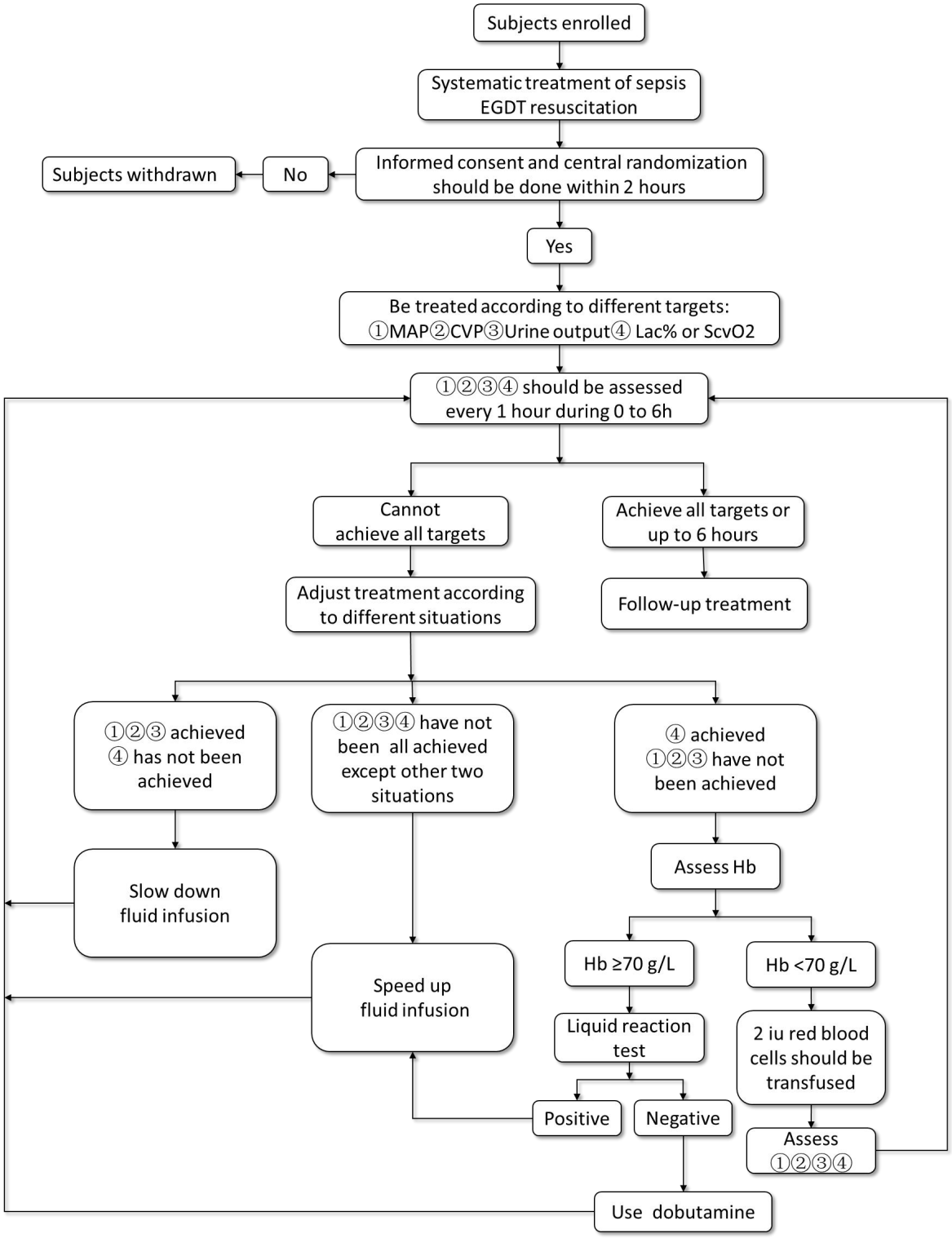
All interventions in each group will be given at the discretion of the clinician according to the targets. The blood-gas analysis, blood lactate and the administration will be registered per hour. In the control group lactate levels were not available for the treatment team and patient during the treatment period. In the Intervention group ScvO2 were not available for the treatment team and patient during the treatment period. This endpoint was to be achieved by a resuscitation strategy as outlined in Figure 1.

Statistical plan and data analysis

The statistical analysis will be done independently by the team of statistical experts. The statistical analysis method is selected according to the purpose of the study, the characteristics of the protocol and the nature of the observation data. Using the chi-square test to study all-cause mortality at 28 days and 90 days, all-cause mortality during hospitalization and ICU stay. The Kaplan-Meier survival curve was used to observe the survival status of the three groups, and the log -rank method to compare the survival of the three groups at 28 days and 90 days whether there is a difference. The multivariate Cox proportional hazards regression model was used to stratify the different factors (gender, age, antibiotic sensitivity, underlying disease type), adjust

covariates, and evaluate the confounding factors at the end of the study. In the sepsis subjects, set three variables for further sub-group analysis: sepsis-induced hyperlipidemia or not, combined adverse reactions， secondary adverse reactions. In order to observe whether the different target-oriented treatment led to the overall supportive treatment intensity and duration of the difference, use variance analysis to analyze the intervention during 0-6h, 0-24h, 0-48h, 0-72h between three groups. If three groups showed a statistical difference, then further comparison between two should be done . In this study, the bilateral test used in the statistical test, α take 0.05, this study using nQuery Adviser 7.0 statistical software.

Figure 1：


Subjects enrolled
Systematic treatment of sepsis EGDT resuscitation
Informed consent and central randomization should be done within 2 hours
No
Subjects withdrawn
Yes
Be treated according to different targets: ①MAP②CVP③Urine output④ Lac% or ScvO2
①②③④ should be assessed every 1 hour during 0 to 6h
Cannot achieve all targets
Achieve all targets or up to 6 hours
Adjust treatment according to different situations
Follow-up treatment
①②③ achieved ④ has not been achieved
①②③④ have not been all achieved except other two situations
④ achieved ①②③ have not been achieved
Slow down fluid infusion
Assess Hb
Hb ≥70 g/L
Hb <70 g/L
Speed up fluid infusion
Liquid reaction test
2 iu red blood cells should be transfused
Positive
Negative
Assess ①②③④
Use dobutamine