■ Title

Tissue perfusion parameter-guided initial resuscitation in adult patients with sepsis or septic shock: A systematic review and network meta-analysis.

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■ Background

Sepsis affects estimated 50 million people and accounts for approximately 11 million death worldwide annually (1). Once sepsis is recognized, immediate treatment and resuscitation is of paramount importance. Sepsis is currently defined as a life-threatening organ dysfunction and/or tissue hypoperfusion due to dysregulated host response to infection (2). As such, fluid resuscitation and vasopressor use are key components of hemodynamic management of patients with possible impaired tissue perfusion or septic shock. After initial fluid resuscitation, where 30 mL/kg of crystalloid solution within 3 h is recommended by the relevant guidelines (3)(4), continuous fluid administration is in general required to restore and maintain organ perfusion. Of note, balanced volume resuscitation is crucial to prevent potential adverse outcomes; excessive resuscitation results in positive fluid balance, leading to pulmonary edema, renal failure, and higher mortality (3)(5). Proper and repetitive assessment of patients' responsiveness to treatment allows clinicians to titrate fluid resuscitation and vasopressor agents. However, substantial question remains regarding what variables we should focus on to optimize organ perfusion.

To date, measuring blood lactate levels is a standardized first step for patients with suspected sepsis or septic shock as it is one of the essential components of the definition of septic shock (2). However, a weak recommendation with low-quality evidence was issued in terms of lactate-guided therapy during initial resuscitation (3), since hyperlactatemia is not necessarily indicative of tissue hypoperfusion (6). Meanwhile, central venous oxygen saturation (ScvO2) was exclusively targeted in the trial of early goal-directed therapy (EGDT), which was not associated with better outcomes compared with usual care (7). Possibly related to this observation, a previous meta-analysis demonstrated superiority of lactate-guided therapy to ScvO2-guided one (8), although sufficiently applicable protocol using lactate clearance is still lacking (9). Furthermore, the veno-

arterial difference in the partial pressure of carbon dioxide or PCO2 gap has been suggested as potentially more reliable substitute to ScvO2 or blood lactate to reflect tissue hypoperfusion (10). More recently, a large randomized clinical trial comparing a peripheral perfusion-targeted strategy, in which capillary refill time (CRT) was evaluated, and lactate-targeted strategy revealed that the CRT group had significantly lower Sequential Organ Failure Assessment (SOFA) score at 72 hours post randomization and a trend towards lower 28-day mortality was observed in the CRT group (11).

Summarizing current evidence on variables for organ perfusion to guide initial resuscitation in sepsis is deemed warranted, given the lack of available data on this topic. Accordingly, we conducted this network meta-analysis (NMA) to examine whether and which tissue perfusion parameter-guided therapy during initial resuscitation in adult patients with sepsis or septic shock improved patients' outcomes.

■ Review question

Does tissue perfusion parameter-guided therapy for initial resuscitation of adult patients with sepsis or septic shock improve outcomes?

■ Searches

We will search the following electronic bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE via PubMed, Web of Science and Igaku-Chuo-Zasshi. Igaku-Chuo-Zasshi is a database of Japanese research papers. We will also search the World Health Organization International Clinical Trials platforms Search Portal (ICTRP) and ClinicalTrials.gov. for ongoing trials. There will be no language restriction.

The search will be performed using the following terms and combinations of related terms.
"systemic inflammatory response syndrome"[MeSH Terms]
"shock, septic"[MeSH Terms]
"multiple organ failure"[MeSH Terms]
"lactates"[MeSH Terms]
"early goal-directed therapy"[MeSH Terms]
"capillaries"[MeSH Terms]
"oxygen saturation"[MeSH Terms]

■ Condition or domain being studied

Patients with sepsis or septic shock.

■ Participants/population

a) Adult (18 years of age or above).
b) Sepsis or septic shock.

■ Intervention, exposure

We will include trials evaluating at least one of the following tissue perfusion parameter-guided therapy: lactate/lactate clearance, capillary refill time, ScvO2/SvO2, and P(v-a)CO2/C(a-v)O2. Early goal-directed therapy (EGDT) will be considered as ScvO2-guided therapy.

■ Comparator/control

We will include any trials evaluating head-to-head comparisons with different parameters above, or with usual care without using any specific tissue perfusion parameter.

- **Types of study to be included**

Randomized controlled trials (RCTs). Quasi-RCTs and non-randomized studies will be excluded.

- **Main outcomes**

a) Mortality.

- **Measures of effect**

Mortality available up to 90 days. If the number of mortality days is not reported, we will substitute in-hospital mortality.

- **Additional outcome**

a) ICU length of stay.
b) ICU mortality.
c) Ventilator free days.

- **Data extraction (selection and coding)**

The process for data extraction will follow Cochrane's recommendations. Two independent reviewers select studies and collect data using a standardized data extraction form as follows:
a) Study characterization: Author, publication year, study design, number of participants of all in study, inclusion criteria, exclusion criteria.
b) Method: Treatment schedules in intervention group and comparison group.
c) Outcome: Measurements and statistics of each outcome, number of participants of each arm.

If the two independent reviewers have a disagreement during the data extraction process, the third reviewer will resolve it.

- **Risk of bias (quality) assessment**

The Cochrane risk of bias 2.0 tool will be used to assess the quality of the study design and the degree of potential bias. The overall quality of evidence with network meta-analysis will be evaluated using the Confidence In Network Meta-analysis (CINeMA) approach.

- **Strategy for data synthesis**

Two types of meta-analysis are planned.

First, direct pairwise meta-analysis will be conducted using RevMan 5.4. We will use random effect models to estimate study-specific effects. Heterogeneity will be assessed using Cochran Q and I2 statistics in accordance with the Cochrane Handbook for Systematic Reviews.

Second, network comparison meta-analysis will be conducted using a frequentist approach with multivariate random effect meta-analysis. This analysis will be performed using STATA MP software (version 17.0; StataCorp, LLC, College Station, TX, United States). In this analysis, categorical data will be estimated by the risk ratio (RR) with 95% confidence intervals and continuous data will be estimated by the mean difference (MD). Where necessary, transformations between risk ratios and odds ratios will be implemented based on overall proportions of events. In addition, the surface under the cumulative ranking curve (SUCRA) will be used to determine the therapy hierarchy.

- **Analysis of subgroup or subsets**

To assess conceptual and statistical heterogeneity, analyses will be conducted for subgroups excluding studies comparing EGDT vs. usual care and at high risk of bias. A post hoc sensitivity analysis will be performed as needed.

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■ Conflict of interest

None.

■ Country

Japan.

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