INTRODUCTION

Severe sepsis and septic shock are complex systemic responses to infection and have immunologic, cardiovascular, and pulmonal implications. There have been numerous treatment strategies aimed at reversing pathophysiologic derangement in sepsis patients. Since its introduction in a landmark trial in 2001,1 goal-directed therapy (GDT) has demonstrated significant survival benefits in sepsis. GDT focuses on the early initiation of monitoring measurements such as central venous pressure and lactate levels, as well as therapeutic maneuvers involving fluid, vasopressors, and transfusion. It was thus a reasonable decision to adopt early GDT in the Surviving Sepsis Campaign (SSC) international guidelines due to the accumulation of clinical evidence of its benefits.2,3 However, this method of treating patients with sepsis has been challenged by several recent multicenter trials. The ARISE trial4 randomized 1600 early septic-shock patients divided into GDT and usual-care groups. The investigators found that there

Protocol-Based Resuscitation for Septic Shock: A Meta-Analysis of Randomized Trials and Observational Studies

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Purpose: Owing to the recommendations of the Surviving Sepsis Campaign guidelines, protocol-based resuscitation or goal-directed therapy (GDT) is broadly advocated for the treatment of septic shock. However, the most recently published trials showed no survival benefit from protocol-based resuscitation in septic shock patients. Hence, we aimed to assess the effect of GDT on clinical outcomes in such patients.

Materials and Methods: We performed a systematic review that included a meta-analysis. We used electronic search engines including PubMed, Embase, and the Cochrane database to find studies comparing protocol-based GDT to common or standard care in patients with septic shock and severe sepsis.

Results: A total of 13269 septic shock patients in 24 studies were included [12 randomized controlled trials (RCTs) and 12 observational studies]. The overall mortality odds ratio (OR) [95% confidence interval (CI)] for GDT versus conventional care was 0.746 (0.631–0.883). In RCTs only, the mortality OR (95% CI) for GDT versus conventional care in the meta-analysis was 0.93 (0.75–1.16). The beneficial effect of GDT decreased as more recent studies were added in an alternative, cumulative meta-analysis. No significant publication bias was found.

Conclusion: The result of this meta-analysis suggests that GDT reduces mortality in patients with severe sepsis or septic shock. However, our cumulative meta-analysis revealed that the reduction of mortality risk was diminished as more recent studies were added.

Key Words: Sepsis, septic shock, shock, meta-analysis
was no significant difference in 90-day mortality, duration of organ support, and length of hospital stay. Another multicenter trial comparing GDT to standard care was the ProCESS study, which showed no differences in 90-day and 1-year all-cause mortality or in the need for organ support; this outcome was similar to that of the ARISE trial.

To evaluate the effect of GDT on mortality risk reduction, two meta-analyses were recently published. One advocated for the survival benefit of GDT, while the other showed conflicting results with no difference observed in survival; in fact, an even worse outcome was associated with GDT in the early-lactate clearance subgroup of patients.

Given such inconsistent results, we conducted a meta-analysis that included the most recent trials of GDT in patients with sepsis. In particular, we assessed the time-dependent changes in risk reduction of GDT by performing a cumulative meta-analysis.

MATERIALS AND METHODS

Ethics committee approval and patient informed consent were not required, as we conducted a meta-analysis of previously published studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook of Systematic Review of Interventions to perform the study.

Literature search
Two authors (Lee and Kim) independently conducted searches in PubMed, Embase, and the Cochrane Register of Controlled Trials databases during the period between the March 20, 2015 and the May 30, 2015 to identify all randomized clinical trials involving GDT in human subjects with septic shock. Search terms were “sepsis,” “shock,” “septic,” “early goal-directed therapy,” “EGDT,” “central venous oxygen saturation,” and “goal-directed resuscitation.” Studies published from January 1992 to May 2015 were additionally included.

We also screened the references included in the articles and published systematic reviews during the same periods to identify other potentially eligible studies.

Inclusion criteria
We included prospective clinical trials conducted in adult patient populations with septic shock. Adults were defined as being over 17 years of age. The intervention was required to comprise GDT, defined as an explicit protocol encompassing the use of hemodynamic monitoring as well as manipulation of hemodynamic parameters to achieve predetermined hemodynamic endpoints. The goals regarding the hemodynamic parameters were different depending on the trials. We defined GDT as a treatment with a specific hemodynamic goal. We only included studies reporting mortality and excluded those reporting only physiological endpoints. Only English-language publications were reviewed.

Quality assessment
The quality of the included studies was determined by two independent assessors who had no role in the design, conduct, analysis, or reporting of any of the included studies. The Cochrane Collaboration tool was used to assess the risk of bias for the randomized studies across the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias.

The RoBANS Tool 9 was used to assess the risk of bias for the observational, non-randomized studies across the following domains: selection of participants (selection bias), confounding variables (selection bias), measurement of intervention (performance bias), blinding for outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias).

Outcome measures
The primary outcome was overall mortality. If the study reported mortality at one time-point, we used only the data provided in the study for our analysis. If the study authors reported mortality at more than one time-point, we preferentially used hospital mortality data. Overall mortality was the only measure we used to compare the efficacy of GDT.
### Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study

| Study                | Year | Study type               | Initiation of enrollment | No. of patients (GDT/control) | Study population                      | Clinical setting | Goals in GDT group | Goals in control group | Timing of GDT | Endpoint               |
|----------------------|------|--------------------------|--------------------------|-------------------------------|---------------------------------------|-----------------|---------------------|------------------------|----------------|------------------------|
| Tuchschmidt, et al.  | 1992 | RCT                      | Unknown                  | 26/25                         | Adult patients with septic shock      | ICU             | CI > 6 L/min/m², SBP > 90 mm Hg | CI > 3 L/min/m², SBP > 90 mm Hg | 6 hrs         | Hospital mortality     |
| Yu, et al.           | 1993 | RCT                      | Unknown                  | 30/22                         | Adult patients with sepsis or septic shock | ICU             | DO² > 600 mL/min/m², SBP > 100 mm Hg | DO² (450-550 mL/min/m²) | 24 hrs        | 30 days mortality      |
| Hayes, et al.        | 1994 | RCT                      | Unknown                  | 50/50                         | Adult patients with septic shock      | ICU             | CI > 4.5 L/min/m², DO² > 600 mL/min/m² | DO² > 450-550 mL/min/m² | Unclear       | ICU mortality          |
| Gattinoni, et al.    | 1995 | RCT                      | 1991                     | 124/57                        | Adult patients with septic shock or septic syndrome | ICU             | CI > 4.5 L/min/m² or SVo² > 70%, MAP 65–90 mm Hg, CVP 8–12 mm Hg, UO > 0.5 mL/kg/hr | CI 2.5–3.5 L/min/m², MAP 65–90 mm Hg, CVP 8–12 mm Hg, UO > 0.5 mL/kg/hr | Unclear       | 180 days mortality     |
| Alía, et al.         | 1999 | RCT                      | 1993                     | 31/32                         | Adult patients with severe sepsis or septic shock | ICU             | DO² > 600 mL/min/m², MAP > 60 mm Hg | DO² > 330 mL/min/m², MAP > 60 mm Hg | Unclear       | ICU mortality          |
| Rivers, et al.       | 2001 | RCT                      | 1997                     | 130/133                       | Adult patients with severe sepsis, septic shock or sepsis syndrome | ED              | SvO² > 70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | 6 hrs         | Hospital mortality     |
| Gao, et al.          | 2005 | Prospective observational | 2004                     | 52/49                         | Adult patients with septic shock      | Ward ICU        | Compliant to EGDT protocol; SvO² > 70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | Noncompliant to EGDT protocol | 6 hrs         | Hospital mortality     |
| Micek, et al.        | 2006 | Before and after         | 2004                     | 60/60                         | Adult patients with septic shock      | ICU             | Add an order set for EGDT protocol; SvO² > 70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | Before adding an order set for EGDT protocol | 6 hrs         | Hospital mortality     |
| Lin, et al.          | 2006 | RCT                      | 2003                     | 108/116                       | Adult patients with septic shock      | ICU             | CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | Usual care | 6 hrs         | Hospital mortality     |
| Nguyen, et al.       | 2007 | Prospective observational | 2003                     | 77/253                        | Adult patients with septic shock      | ED              | After education of therapeutic target of EGDT; Scvo² > 70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO > 0.5 mL/kg/hr | Before education of EGDT | 6 hrs         | Hospital mortality     |
Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study (Continued)

| Study                  | Year | Study type          | Initiation of enrollment | No. of patients (GDT/control) | Study population | Clinical setting | Goals in GDT group | Goals in control group | Timing of GDT | Endpoint          |
|------------------------|------|---------------------|--------------------------|-------------------------------|------------------|------------------|--------------------|------------------------|----------------|-------------------|
| Jones, et al.          | 2007 | Prospective interventional | 2005                    | 77/79                         | Adult patients with septic shock | ED               | ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before education of EGDT | 6 hrs          | Hospital mortality |
| Zambon, et al.         | 2008 | Prospective observational | 2005                    | 44/17                         | Adult patients with septic shock | ICU              | Compliant to target of EGDT; ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Not compliant to target of EGDT | 6 hrs          | Hospital mortality |
| Ferrer, et al.         | 2008 | Before and after     | 2006                    | 1465/854                      | Adult patients with septic shock | ICU              | After education of EGDT protocol; ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before education of EGDT protocol | 6 hrs          | Hospital mortality |
| MacRedmond, et al.     | 2010 | Prospective observational cohort | 2008                     | 37/37                         | Adult patients with septic shock | ED               | ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before EGDT protocol | 6 hrs          | Hospital mortality |
| Puskarich, et al.      | 2009 | Before and after     | 2005                    | 206/79                        | Adult patients with septic shock | ED               | ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before EGDT protocol | 6 hrs          | 1 yr mortality     |
| Crowe, et al.          | 2010 | Prospective observational cohort | 2007                     | 183/123                       | Adult patients with septic shock | ED               | ScvO₂ >70% (not continuous) CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before EGDT protocol | 6 hrs          | Hospital mortality |
| De Miguel-Yanes, et al. | 2009 | Observational cohort | 2007                    | 50/53                         | Adult patients with septic shock | ED               | After education of EGDT; ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before education of EGDT | 6 hrs          | Hospital mortality |
| Castellanos-Ortega, et al. | 2010 | Quasi-experimental study | 2005                   | 384/96                        | Adult patients with septic shock | ICU              | After education of EGDT; ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Before education of EGDT | 6 hrs          | Hospital mortality |
| Jones, et al.          | 2010 | RCT                 | 2007                    | 150/150                       | Adult patients with septic shock | ED               | ScvO₂ >70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO >0.5 mL/kg/hr | Lactate clearance CVP>8 mm Hg MBP>65 mm Hg | Unclear        | Hospital mortality |
| Coba, et al.           | 2011 | Prospective cohort  | 2006                    | 64/434                        | Adult patients with septic shock | ED               | Compliant within 6 hrs to EGDT protocol; ScvO₂ 70%, CVP>8 mm Hg, MAP>65 mm Hg | Not compliant | 6 hrs          | Hospital mortality |
Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study (Continued)

| Study | Year | Initiation of enrollment | Study type | No. of patients of patients (GDT/control) | Clinical setting | Study population | Treatment Goals in GDT group | Timing of GDT | Endpoint of the study |
|-------|------|--------------------------|------------|-----------------------------------------|------------------|-----------------|--------------------------|---------------|----------------------|
| Andrews, et al. | 2014 | RCT | 2012 | 59/56 | Adult patients with septic shock | ED | ED | Usual care | Hospital mortality | 6 hrs |
| ARISe | 2014 | RCT | 2012 | 796/804 | Adult patients with septic shock | ED | ED | Usual care | Usual care | 90 days mortality |
| ProCESS | 2012 | RCT | 2014 | 623/620 | Adult patients with septic shock | ED | ED | Usual care | Usual care | 90 days mortality |
| ProMISe22 | 2012 | RCT | 2014 | 439/465 | Adult patients with septic shock | ICU | ICU | Usual care | Usual care | 90 days mortality |

**Statistical analysis**

Whether heterogeneity between study effects was significant or not was evaluated by using the Q statistical value obtained via chi-squared distribution analysis in order to identify appropriate studies. The random effect model was adopted where the p-value of the Q statistic for the accumulated effects was greater than 0.1.7 The odds ratio (OR) along with the 95% confidence interval (CI) of the overall mortality are presented. Publication bias was investigated by using a funnel plot and Egger and Begg’s statistical tests.20,21 The funnel plots did not indicate publication biases, a finding that was further confirmed in the Egger and Begg’s tests, which yielded p-values greater than 0.05. All data analyses were performed using Comprehensive Meta-Analysis version 2.0 (Bios tat, Inc., Englewood, NJ, USA).

**RESULTS**

**Identification of eligible trials**

In the initial search, we identified 4693 articles (Fig. 1). After the removal of 1863 duplicates, we reviewed 1259 titles and abstracts and eliminated 1215 articles not meeting the study inclusion criteria. Two investigators reviewed 44 full-text articles and subsequently excluded 20 that did not meet the inclusion criteria: six articles were reviews or meta-analyses, five were published in Chinese only, four were inappropriate owing to the age range of those studied (i.e., children or geriatric patients), and five were retrospective studies. Randomized controlled trials (RCTs), prospective cohort studies, and before-and-after studies were included in the analysis.

**Characteristics of included trials**

Twenty-four studies fulfilled the inclusion criteria: 12 each of RCTs and non-RCTs. In Table 1, the characteristics of the included trials are summarized. The regions where the studies were performed included the United States, Canada, Spain, Italy, Germany, Taiwan, Africa, and Australia; thus, there was a broad international distribution. The population age targeted by Jones, et al.12 was over 17 years, while that targeted by Hayes, et al.24 was over 21 years. The protocols for GDT were variable. The early studies13-17 targeted the oxygen delivery index, cardiac index, and oxygen consumption. The therapeutic targets of the study by Rivers, et al.1 included SvO2 (mixed venous oxygen saturation) >70, central venous pressure 8-12, and mean arterial pressure >65. The later studies mostly followed the GDT protocol of Rivers, et al.,1 and one of the studies modified the protocol by using lactate instead of SvO2.18 The target time for therapy administration was generally within 6 hours except in five studies; four11,13,15,16 had unclear target times and one14 targeted 24 hours. The years of publication of these studies were between 1992 and 2015.

**Risks of bias in the included studies**

The details of the risks of bias, summarized in Fig. 2, are each
categorized into RCTs and non-RCTs. The RCTs (Fig. 2A) mostly exhibited a low risk of bias, although the risk in two studies was unclear. Although randomized sequences were generated in six trials, while proper randomization was questionable in two studies. None of the RCTs were double-blinded; blinding of patients and clinicians is extremely difficult when treating for septic shock, especially when applying GDT protocols. However, we concluded that the primary outcome (mortality) was seldom influenced by blinding the study. Biases related to reporting were low; other biases were unclear.

Almost all non-RCTs (Fig. 2B) were at high risk of selection bias except in four studies. These four studies were conducted consecutively, and their data were collected prospectively. All non-RCTs were at a high risk of containing confounding variables. Four non-RCTs were before-and-after investigations, while the others were prospective observational studies. We assumed that the learning effects were clear to the researchers when performing the before-and-after studies using the GDT protocol. In the prospective observational studies, major confounders were confirmed, although adjusting for the confounders was difficult. The bias in measurements was relatively low as the primary outcome was patient mortality.

**Overall mortality**

A total of 13269 patients were available for the analysis of our primary endpoint. Overall mortality in the GDT and control groups was 1717 of 5259 patients and 1638 of 4655 patients, re-
Protocol-Based Resuscitation for Septic Shock

spectively. Overall, GDT significantly reduced overall mortality in the random-effects model (OR, 0.746; 95% CI, 0.631–0.883; p-value for heterogeneity <0.0001; I²=57.71%) (Fig. 3). The results of the subgroup analyses are presented in Table 2.

RCT-only meta-analysis

In the subgroup analysis (Table 2), we evaluated RCT studies only. GDT had no benefit regarding overall mortality compared to the results of all studies including non-RCTs (OR, 0.929; 95% CI, 0.747–1.155; p-value for heterogeneity=0.024; I²=50.07%) (Fig. 4). This result contrasted with that of the analysis of all studies.

Cumulative statistics

We indexed the studies based on when each was performed and then categorized them into three groups: 2001–2003, 2004–2007, 2008 or later. This classification was according to the SSC publication update. We then conducted a cumulative meta-analysis. The results revealed that the effectiveness of each GDT was decreasing (Fig. 5) and was

Table 2. Subgroups Based on Study Type and Initiation Year

| Subgroups          | No. of studies | No. of patients | OR (95% CI)   | p value | I² (%) |
|--------------------|----------------|-----------------|---------------|---------|--------|
| All trials         | 24             | 13269           | 0.75 (0.63–0.88) | <0.0001 | 57.71  |
| Study type         |                |                 |               |         |        |
| RCTs               | 12             | 6521            | 0.93 (0.75–1.16) | 0.024   | 50.07  |
| Non-RCTs           | 12             | 6748            | 0.80 (0.48–0.76) | 0.031   | 48.13  |
| Initiation of enrollment |      |                 |               |         |        |
| 2001–2003          | 3              | 817             | 0.66 (0.44–0.98) | 0.041   | 53.31  |
| 2004–2007          | 11             | 4472            | 0.69 (0.55–0.88) | 0.003   | 51.88  |
| 2008–2015          | 5              | 3921            | 1.01 (0.87–1.17) | 0.899   | 23.63  |

RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval.
comparable with the subgroup analysis based on the study initiation year (Fig. 6).

**Subgroup analysis based on the year of enrollment**

In the subgroup analysis (Table 2), we evaluated the initiation year of the study enrollment and grouped studies into three pe-

| Model | Study name | Odds ratio | Lower limit | Upper limit | Z-value | p-value |
|-------|------------|------------|-------------|-------------|---------|---------|
| Fixed | ProMiSe22 | 1.017 | 0.796 | 1.298 | 0.132 | 0.895 |
|       | ProCESS3  | 1.141 | 0.821 | 1.584 | 0.785 | 0.432 |
|       | ARISe4    | 0.988 | 0.768 | 1.271 | -0.097 | 0.922 |
|       | Andrews, et al.21 | 1.158 | 0.533 | 2.517 | 0.370 | 0.711 |
|       | Jones, et al.19 | 1.466 | 0.825 | 2.604 | 1.303 | 0.193 |
|       | Lin, et al.23 | 0.461 | 0.265 | 0.802 | -2.743 | 0.006 |
|       | Rivers, et al.1 | 0.518 | 0.311 | 0.863 | -2.529 | 0.011 |
|       | Alia, et al.17 | 1.506 | 0.508 | 4.461 | 0.739 | 0.460 |
|       | Gattinoni, et al.36 | 1.135 | 0.586 | 2.200 | 0.376 | 0.707 |
|       | Hayes, et al.32 | 1.631 | 0.681 | 3.909 | 1.098 | 0.272 |
|       | Yu, et al.33 | 0.410 | 0.100 | 1.681 | -1.238 | 0.216 |
|       | Tuchschmidt, et al.14 | 0.389 | 0.122 | 1.245 | -1.591 | 0.112 |
| Random | Fixed | 0.963 | 0.846 | 1.097 | -0.568 | 0.570 |
|       | Random | 0.929 | 0.747 | 1.155 | -0.663 | 0.507 |

**Fig. 4.** Forest plot of the effectiveness of goal-directed therapy on overall mortality including only RCTs. RCTs, randomized controlled trials; CI, confidence interval.

| Model | Study name | Odds ratio | Lower limit | Upper limit | Z-value | p-value |
|-------|------------|------------|-------------|-------------|---------|---------|
|       | Lin, et al.29 | 0.461 | 0.265 | 0.802 | | |
|       | Nguyen, et al.26 | 0.433 | 0.288 | 0.651 | | |
|       | Gao, et al.25 | 0.407 | 0.282 | 0.589 | | |
|       | Micke, et al.30 | 0.437 | 0.314 | 0.607 | | |
|       | Jones, et al.12 | 0.461 | 0.340 | 0.623 | | |
|       | Zambon, et al.2 | 0.448 | 0.334 | 0.600 | | |
|       | Puskarich, et al.21 | 0.482 | 0.373 | 0.623 | | |
|       | Castellanos-Ortega, et al.3 | 0.474 | 0.379 | 0.592 | | |
|       | Ferrer, et al.21 | 0.527 | 0.397 | 0.699 | | |
|       | Coba, et al.23 | 0.568 | 0.437 | 0.739 | | |
|       | Crowe, et al.20 | 0.592 | 0.469 | 0.748 | | |
|       | De Miguel-Yanes, et al.28 | 0.601 | 0.482 | 0.750 | | |
|       | Jones, et al.14 | 0.639 | 0.508 | 0.804 | | |
|       | MacRedmond, et al.24 | 0.623 | 0.496 | 0.782 | | |
|       | ARISe4 | 0.658 | 0.533 | 0.813 | | |
|       | ProCESS3 | 0.692 | 0.565 | 0.848 | | |
|       | ProMiSe22 | 0.722 | 0.599 | 0.870 | | |
|       | Andrews, et al.21 | 0.736 | 0.614 | 0.882 | | |
| Random | Fixed | 0.736 | 0.614 | 0.882 | | |
|       | Random | 0.929 | 0.747 | 1.155 | -0.663 | 0.507 |

**Fig. 5.** Cumulative forest plot of RCTs and non-RCTs published after 2001. RCTs, randomized controlled trials; CI, confidence interval.
riods; period 1, before 2003; period 2, 2004–2007; and period 3, 2008–2015. This categorization was to analyze the change of clinical performance with time passage, and the results showed that the ORs approached values of 1 as time progressed (period 1, 0.661; period 2, 0.693; period 3, 1.010). We surmised that the difference between the effectiveness of GDT and usual care has decreased since 2001, simultaneously with the introduction of EGDT. Table 3 shows the amount of fluid administration within the first 6 hours in the recent RCTs. In the most recent study, the amount of fluid administration was not statistically different between the two groups, GDT and usual care.

**Publication bias**

We detected no evidence of publication bias as determined by the funnel plot both visually (Fig. 7) and statistically (p=0.359 by the Begg’s test); we also checked the RCTs alone (p=0.837 using Begg’s test) (Fig. 8).

**DISCUSSION**

In this meta-analysis, 12 RCTs and 12 non-RCTs were analyzed to compare overall mortality between GDT and non-GDT strategies. GDT remains an effective treatment modality for reducing the mortality rate among septic shock patients. Prospective and retrospective studies accumulated over the years verify the efficacy of the GDT protocol in reducing mortality among patients in septic shock. However, the differences in outcome between GDT and standard care have been decreasing according to recent trials.

A concrete form of GDT focusing on early therapeutic measures involving fluid, vasopressors, and transfusion to meet pre-
Table 3. The Amount of Fluid Administration for First 6 Hours, Unit Is Presented As mL (Mean ± Standard Deviation)

| Author (study period) | EGDT   | Control | p value |
|-----------------------|--------|---------|---------|
| ProCESS (2011–2014)   | 2805±1957 | 2783±1880 | 0.818   |
| ARiSe (2008–2014)     | 1964±1415 | 1713±1401 | 0.004*  |
| ProMISe (2008–2013)   | 2226±1443 | 2022±1271 | 0.001*  |

EGDT, early goal-directed therapy. *Statistically significant, p value<0.05.

Fig. 7. Funnel plot of overall trials, RCTs and non-RCTs (p value=0.359). RCTs, randomized controlled trials.

Fig. 8. Funnel plot of RCTs (p value=0.837). RCTs, randomized controlled trials.

specified targets was introduced by a highly influential single-center trial performed by Rivers et al., although its primitive resuscitation protocol had been attempted beforehand. They administered approximately 5 liters of fluid in the first 6 hours of resuscitation, resulting in a 16% improvement of inhospital survival in severe sepsis and septic shock patients.

Although the efficacy of GDT remains a matter of debate, it has been rapidly integrated into clinical practice as a form of the sepsis bundle due to its definite survival benefit, and its clinical efficacy was established via subsequent trials. In recent years, it has become less apparent whether GDT has any advantage for survival of patients with severe sepsis. Investigators who published the latest meta-analyses, including RCTs, have already pronounced the end of the GDT era. However, further research is required to identify the efficacy of GDT for resuscitation of patients with sepsis and to re-evaluate the effect of GDT in clinical practice.

In our study, GDT showed no additional efficacy when analyzing RCTs only. However, in the overall analysis of prospective studies, including observational studies, GDT is effective in reducing mortality in sepsis patients. This finding is striking, as heterogeneous results from RCTs and observational studies could be the reason for detecting inconsistent effects of GDT in sepsis patients. The most recent meta-analysis of RCTs failed to show a survival benefit with GDT, although GDT effectively reduced mortality in sepsis patients according to the meta-analysis published prior to the recent large multicenter trials.

There are several possible explanations as to why the clinical benefit of GDT is diminishing in the more recent trials. As we observed in the present analysis, the amount of fluid administration (Table 3) between standard-care and GDT groups in the most recent RCT (study period: 2011–2014) was not significantly different, compared with other two prior RCTs (Table 3). Since GDT was integrated into the SSC guidelines, it has been widely adopted as a part of sepsis care, and healthcare professionals involved in the recent trials were very familiar with GDT practices. We surmise that this is why the amount of fluid was not different between the standard-care and GDT groups with the passage of time.

We also noted the issue of the time of study enrollment, which is the reason why we conducted a cumulative meta-analysis to assess the time-dependent changes in risk reduction of GDT in sepsis patients. Subgroup analysis according to the actual period of the trial enrollment was performed. There are always time intervals between the year of enrollment and study publication; a clinical trial of patients with septic shock is extensive and can span many years. The actual clinical practices in the field are always changing; therefore, methods in more recent publications will differ from those of previous years. We assumed that the GDT protocol set in the year of the initiation of the trial reflected the skill and methodology trends of the clinical staff in that particular year. Hence, in addition to our main analysis, we arranged the trials chronologically according to the year of initiation of study enrollment and performed a cumulative analysis (Fig. 5), which showed that the 95% CIs of the ORs were surpassed as more recent trials were included. The comparison of the amount of fluid administration in Table 3 also indicates that the usual care is changing. The fluid management of usual care seems to be becoming similar to the fluid administration of GDT. However, we cannot hastily conclude that usual care is identical to GDT care based on this data alone.

A limitation of our study was that we included RCTs and non-RCTs together. We therefore could not dismiss the heterogeneity of this study. In Table 2, the overall I² value was 57.71% for all trials, which suggests that there is heterogeneity amongst the included trials; therefore, it cannot be ruled out that heterogeneity may have affected the results of the analysis. In critical care settings, it is extremely difficult to perform randomized studies; hence, there are numerous prospective observational studies evaluating the effectiveness of GDT.
Additionally, as we aimed to investigate the effectiveness of GDT, the treatment duration goal was heterogeneous. In a subgroup analysis that includes the initiation of the study enrollment, the year cannot reflect the entire eligibility period of a trial. Even during study enrollment, the clinical performance of the medical staff can progress, regress, or change. When arranging the trials chronologically according to the initiation year, such performance changes were not taken into account.

In summary, this meta-analysis suggests that GDT reduces mortality in patients with severe sepsis or septic shock. However, a cumulative meta-analysis revealed that the effect of risk reduction decreased as more recent studies were incorporated. Additional investigation is required prior to making definitive recommendations with respect to the effect of GDT on the resuscitation of patients with sepsis.

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