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The effect of early goal-directed therapy for treatment of severe sepsis or septic shock: A systemic review and meta-analysis☆,☆☆

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ABSTRACT

Purpose: To assess the effects of early goal-directed therapy (EGDT) on reducing mortality compared with conventional management of severe sepsis or septic shock.
Materials and methods: We included a systemic review, using the Medline and EMBASE. Seventeen randomized trials with 5765 patients comparing EGDT with usual care were included.
Results: There were no significant differences in mortality between EGDT and control groups (relative risk [RR], 0.89; 95% confidence interval [CI], 0.79-1.00), with moderate heterogeneity ($I^2 = 56\%$). The EGDT was associated with lower mortality rates when the mortality rate of the usual care group was greater than 30% (12 trials; RR, 0.83; 95% CI, 0.72-0.96), but not when the mortality rate in the usual care group was less than 30% (5 trials; RR, 1.03; 95% CI, 0.92-1.16). The mortality benefit was seen only in subgroup of population analyzed between publication of the 2004 and 2012 Surviving Sepsis Campaign guidelines, but not before and after these publications.
Conclusion: This meta-analysis was heavily influenced by the recent addition of the trio of trials published after 2014. The results of the recent trio of trials may be biased due to methodological issues. This includes lack of blinding by incorporating similar diagnostic and therapeutic interventions as the original EGDT trial.

1. Introduction

Severe sepsis and septic shock are common and fatal complications of patients with chronic illness and acute organ dysfunction secondary to infection [1]. The incidence of severe sepsis and septic shock in adults ranges from 56 to 91 per 100 000 population per year [2]. The short-term mortality is 20% to 30%, and up to 50% in patients with septic shock [1,3]. In 2001, Rivers et al [4] reported that early goal-directed therapy (EGDT) reduced short-term mortality in patients with severe sepsis or septic shock. The EGDT was composed of early identification of high-risk patients, appropriate cultures, source control, and administration of appropriate antibiotics, which was followed by early hemodynamic optimization of oxygen delivery and decreasing oxygen consumption. Subsequently, EGDT was incorporated into the Surviving Sepsis Campaign (SSC) guidelines [5-8], and studies through 2010 reported improved survival with EGDT [9-11].

However, despite the SSC guidelines, EGDT has not been widely implemented due to concerns about its generalizability as a single-center study [12]. To address these concerns, 3 large, multicenter randomized controlled trials (RCTs) were performed in the United States, Australia, and the United Kingdom and published in 2014 and 2015 [13-16]. However, these studies failed to find any mortality benefit associated with EGDT, and questioned the systematic use of EGDT for management of patients with septic shock and the incorporation of EGDT into the SSC guidelines. These studies were criticized for being underpowered and posing a risk of false-negative results [17]. After publication of recent trio trials, numerous meta-analyses of EGDT have attempted to determine whether EGDT improves outcomes in patients with sepsis [11,18-31]. However, the pooled analysis results have been inconsistent due to different methodologies and reasonable explanation of substantial heterogeneity has not been evaluated fully.

Thus, we sought to systematically review previously published RCTs including these 3 recent RCTs, which assessed EGDT for management of patients with severe sepsis or septic shock. Our second objective was to

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use subgroup analysis to propose reasonable explanations for these discordant study findings.

2. Materials and methods

This systemic review and meta-analysis was performed according to recommendations from the Cochrane Handbook for Systemic Reviews of Interventions [32] and the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statements [33]. The research question was formulated according to the Participants, Interventions, Comparisons and Outcome model: P, adult patients with severe sepsis or septic shock; I, EGDT, defined on the basis of the "Rivers protocol"; C, non-EGDT usual care; O, short-term mortality.

2.1. Eligibility criteria

We included only RCTs conducted in adult patients with severe sepsis or septic shock that compared EGDT with either usual care or another resuscitation strategy that did not include EGDT. The EGDT was defined according to Rivers et al as protocolized resuscitation to achieve predetermined hemodynamic goals. Only studies that reported sufficient data, including mortality, to calculate a relative risk (RR) were included.

2.2. Search strategy

Two authors (WHK, SS) independently conducted searches of Medline via the PUBMED interface, EMBASE databases, and reference lists of the extracted articles from inception to May 2015. The same authors independently reviewed the titles and abstracts of all studies found by the search to identify eligible trials. We also screened the reference lists of previous systemic reviews for the same period [5-7,11,12,18-28].

The search strategy was: (((((((sepsis) OR septicemia) OR septic shock) OR severe sepsis) OR blood stream infection) OR endotoxic shock) OR toxic shock OR critically ill patients)) AND ((((((((((egdt) OR early goal-directed therapy) OR early goal therapy) OR early directed therapy) OR goal-oriented) OR protocol directed therapy) OR goal-directed therapy) OR goal directed therapy) OR rivers protocol) OR oxygen delivery) AND ((((((randomized controlled trial) OR controlled clinical trial) OR randomized) OR randomly) OR trial) OR groups).

2.3. Data extraction

The following information was extracted from each trial: study first author, year of publication, number of enrolled patients (EGDT and control), study population, clinical setting, hemodynamic goals in EGDT and control groups, mortality end point, study design, and outcome data.

2.4. Assessment of risk of bias

We assessed the risk of bias of individual studies using the bias domains described in the Cochrane Handbook for Systemic Reviews of Interventions, version 5.1.0 [32]. Two authors (WHK, SS) independently and subjectively reviewed all studies and assigned a judgment of "high", "low", or "unclear" risk of bias for individual studies across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Disagreement was resolved by discussion between the 2 assessors and a third outside assessor (HSS), who provided arbitration.

2.5. Outcome definitions

The prespecified primary outcome was overall mortality. If mortality was reported at only one time point, only that data were included in the analysis. If mortality was reported at more than 1 time point, the mortality identified as the primary outcome for that study was used for analysis.

2.6. Statistical analysis

A random-effect model (Mantel–Haenszel method) was used to estimate the effect size for the primary outcome, expressed as a pooled RR with 95% confidence interval (CI), and a forest plot. A sensitivity analysis using a fixed effect model was also conducted. I^2 statistics were used to assess statistical heterogeneity across studies [34,35]. Predefined subgroup analysis was conducted based on the publication date and mortality rates of the usual care groups. Publication bias was analyzed by inspection of funnel plots as well as Egger test [36]. Data analysis was performed using Review Manager 5.2 (RevMan; The Cochrane Collaboration, Oxford, United Kingdom) and Stata/SE version 14.0 (StataCorp, College Station, Texas, USA). A 2-sided *P* value of 0.05 or less was considered statistically significant.

3. Results

3.1. Eligible studies

Fig. 1 shows the search results and reasons for exclusion from the current study. After screening 2001 titles and abstracts, 133 duplicate studies and 1707 articles not meeting the inclusion criteria were eliminated. No additional studies were obtained from the Cochrane trial register or from bibliographic search of relevant articles. After carefully reviewing the full text of the remaining 161 trials, 144 were excluded as reviews (n = 74); statistical analysis plans of enrolled trials (n = 5); not including sepsis diagnosis (n = 19); not RCT (n = 27); pediatric studies (n = 5); different EGDT protocols (n = 11); and lack of mortality data (n = 3). Finally, 17 RCTs comparing EGDT with usual care for severe sepsis or septic shock were included [4,9,13-15,37-48]. There was 100% agreement between the 2 reviewers on study inclusion and exclusion.

3.2. Study characteristics

The study characteristics are summarized in Supplemental Table 1. The trials were published between 1992 and 2015 and included a total number of 2917 and 2848 patients in EGDT and usual care groups, respectively. Four articles were in Chinese [43-46], and other 11 trials were in English. We referred to a previous meta-analysis including these 4 RCTs for mortality data and risk of bias assessment [21].

3.3. Risk of bias among included studies

The details of the assessment of risk of bias are summarized in Supplemental Fig. 1. Only the original EGDT trial was judged to be at low risk of bias [4], whereas the other 16 trials were judged to be at high risk of bias [9,13-15,37-48]. Twelve trials generated adequate randomized sequences [4,9,13-15,38-40,42,46-48], and 9 generated appropriate allocation concealment [4,9,13-15,40,42,47,48]. None of the 17 RCTs were double-blinded. Only the original EGDT trial was blinded to the personnel [4], because it was emergency department–based trial and all other studies were intensive care unit (ICU)-based trials. In the original EGDT trial, ICU personnel were effectively blinded to the group assignments during emergency department. Furthermore, the ICU management team did not use lactate levels or central venous oxygen saturation ($Scvo_2$) in their clinical practice.

3.4. Primary outcome: overall mortality

A total of 5765 patients were available for analysis of our primary outcome. The overall mortalities in the EGDT and usual care groups were 877 among 2917 (30.1%) and 913 among 2848 (32.1%),

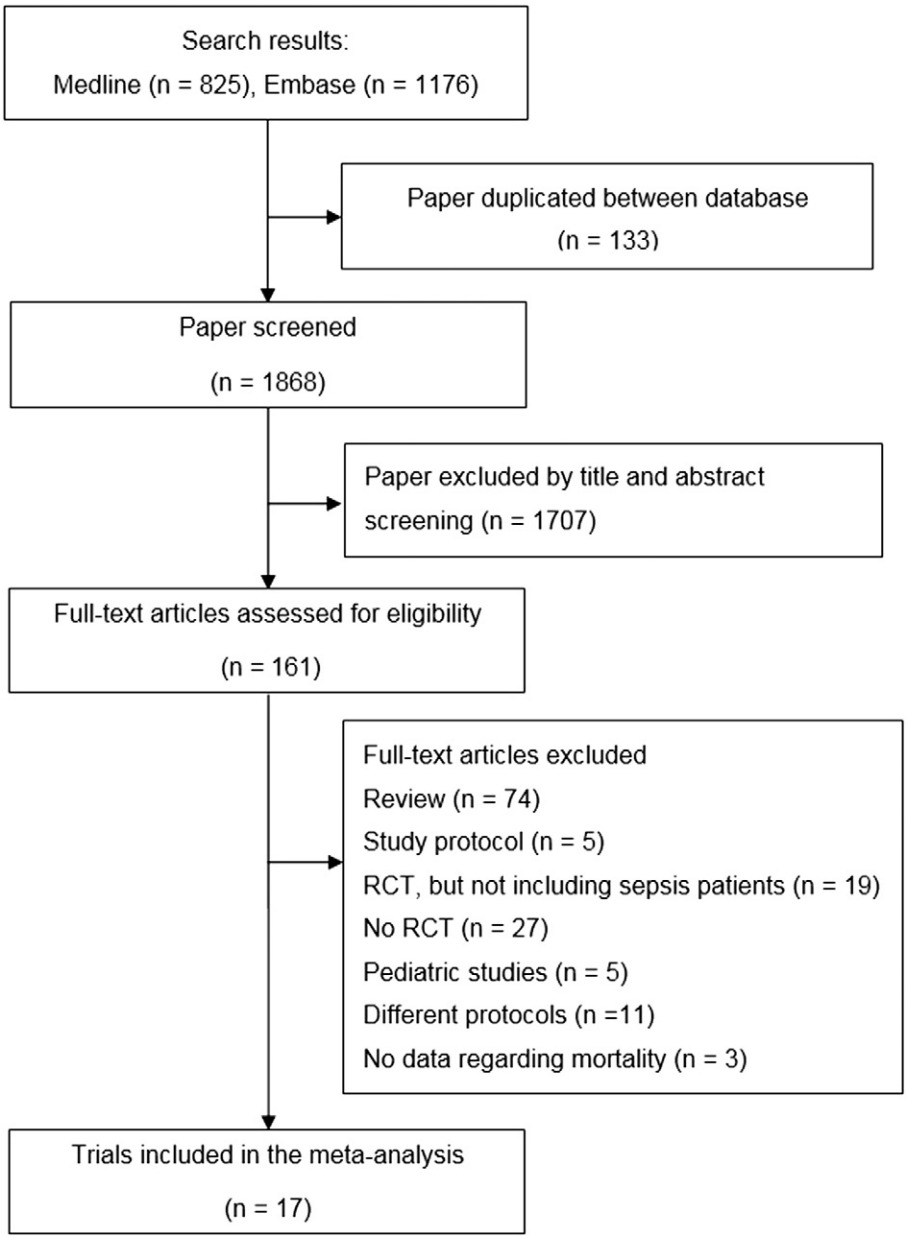

Fig. 1. Search strategy flow diagram.

respectively. As shown in Fig. 2, pooled analyses of all enrolled RCTs showed that EGDT did not reduce overall mortality in the random-effect model (RR, 0.89; 95% CI, 0.79-1.00; $P = .05$), with evidence of moderate to substantial heterogeneity ($\chi^2 = 36.76$, $I^2 = 56\%$).

Subgroup analysis according to mortality category (greater and less than 30%) revealed that EGDT was associated with lower mortality rate in comparison with the usual care group when mortality rate of the usual care group was greater than 30% (12 trials; RR, 0.83; 95% CI, 0.72-0.96; $P = .005$; $I^2 = 59\%$), but not when the mortality rate in the usual care was less than 30% (5 trials; RR, 1.03; 95% CI, 0.92-1.16; $P = .59$; $I^2 = 0\%$) (Fig. 3).

Subgroup analysis according to the publication years of the SSC guidelines suggested that the mortality benefit was seen only in the subgroup of RCTs published between the publication of the 2004 and 2012 SSC guidelines (6 trials; RR, 0.78; 95% CI, 0.66-0.92; $P = .03$; $I^2 = 32\%$), but not in the subgroup of RCTs published before the publication of the 2004 SSC guidelines and after 2012 SSC guidelines (before SSC 2004, 7 trials; RR, 0.85; 95% CI, 0.65-1.11; $P = .22$; $I^2 = 66\%$; after SSC 2012, 4 trials; RR, 1.03; 95% CI, 0.93-1.15; $P = .55$; $I^2 = 0\%$) (Fig. 4).

3.5. Publication bias

Visual and statistical assessment of funnel plots revealed no evidence of publication bias ($P = .487$ by Egger test, $P = .773$ by Begg test) (Supplemental Fig. 2).

4. Discussion

This meta-analysis demonstrated that the results of trials investigating the effect of EGDT in septic shock have shown significant mortality benefit only when the mortality of the group receiving usual care was more than 30%. The results also showed that EGDT had significant mortality benefits between the publication of the 2004 and 2012 SSC guidelines. These findings suggest that usual care has evolved and mortality

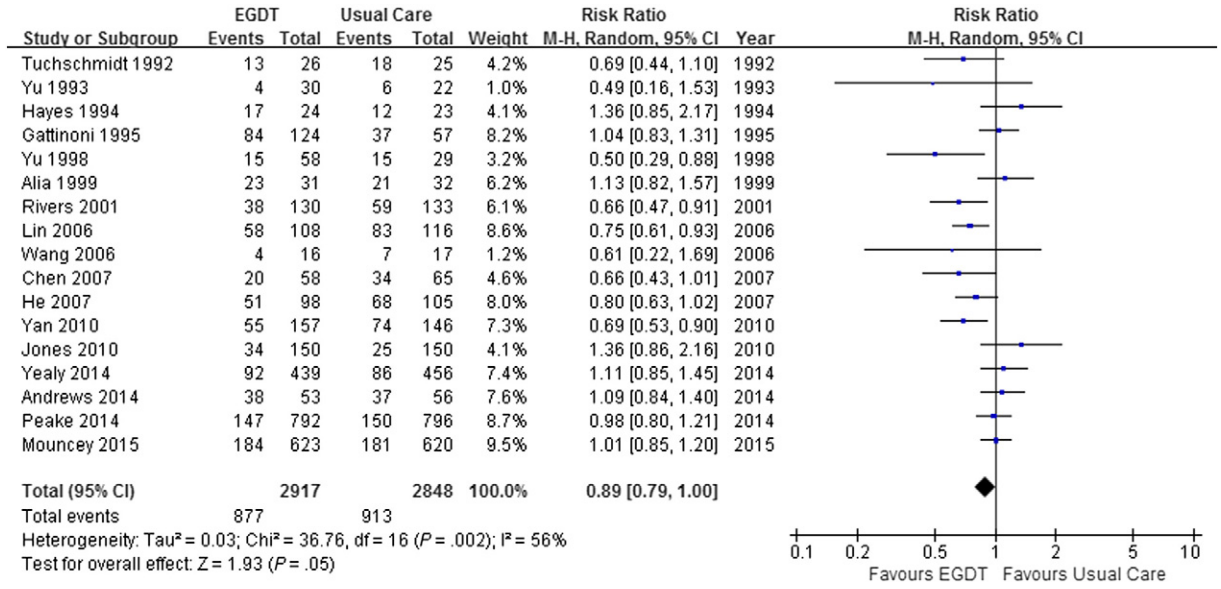

Fig. 2. Effect of EGDT in protocol and usual care groups on mortality rate. M-H, Mantel–Haenszel.

rates have decreased with increasing compliance of the SSC guidelines. Therefore, the negative results of recent 3 trials evaluating the effects of EGDT should not be interpreted as a failure of EGDT but, rather, appears to be results of biases from improvement of usual care and methodological factors.

Recently published results from the Protocol-based Care for Early Septic Shock (ProCESS), Austrailian Resuscitation In Sepsis Evaluation (ARISE), and Protocolized Management In Sepsis (ProMISe) trials suggest that EGDT with routine placement of a central venous catheter and $Scvo_2$ monitoring does not longer improve outcomes in patients with septic shock [13-15]. These studies only tested the impact of the specific EGDT algorithm proposed by Rivers et al [4] and had numerous methodological issues including no blinding to ICU personnel. The mortality of septic shock was less than 30% in all 3 trials, which may suggest that the resuscitation bundles of SSC including EGDT have been integrated into daily clinical practices. Therefore, the results of these recent

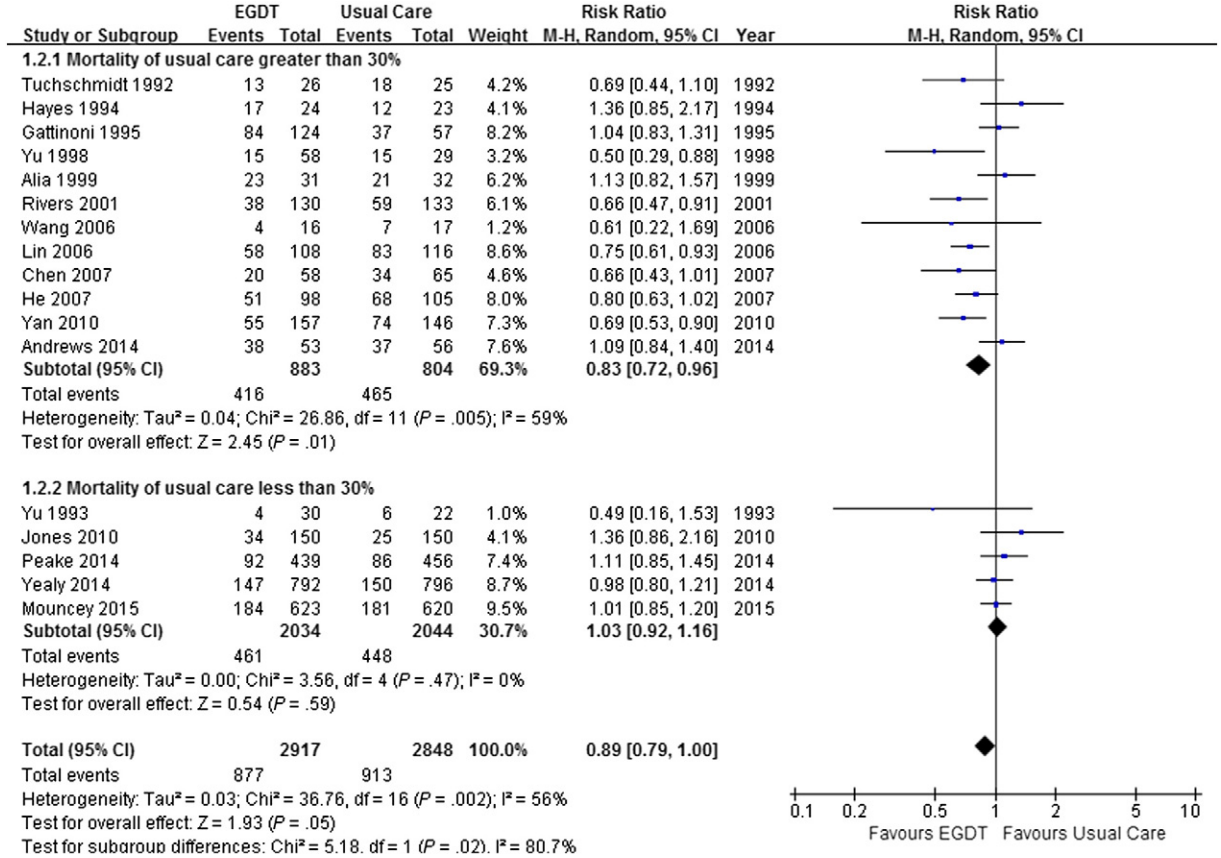

Fig. 3. Comparison of the effect of EGDT in the protocol and usual care groups on mortality rate according to usual care group mortality rates. M-H, Mantel–Haenszel.

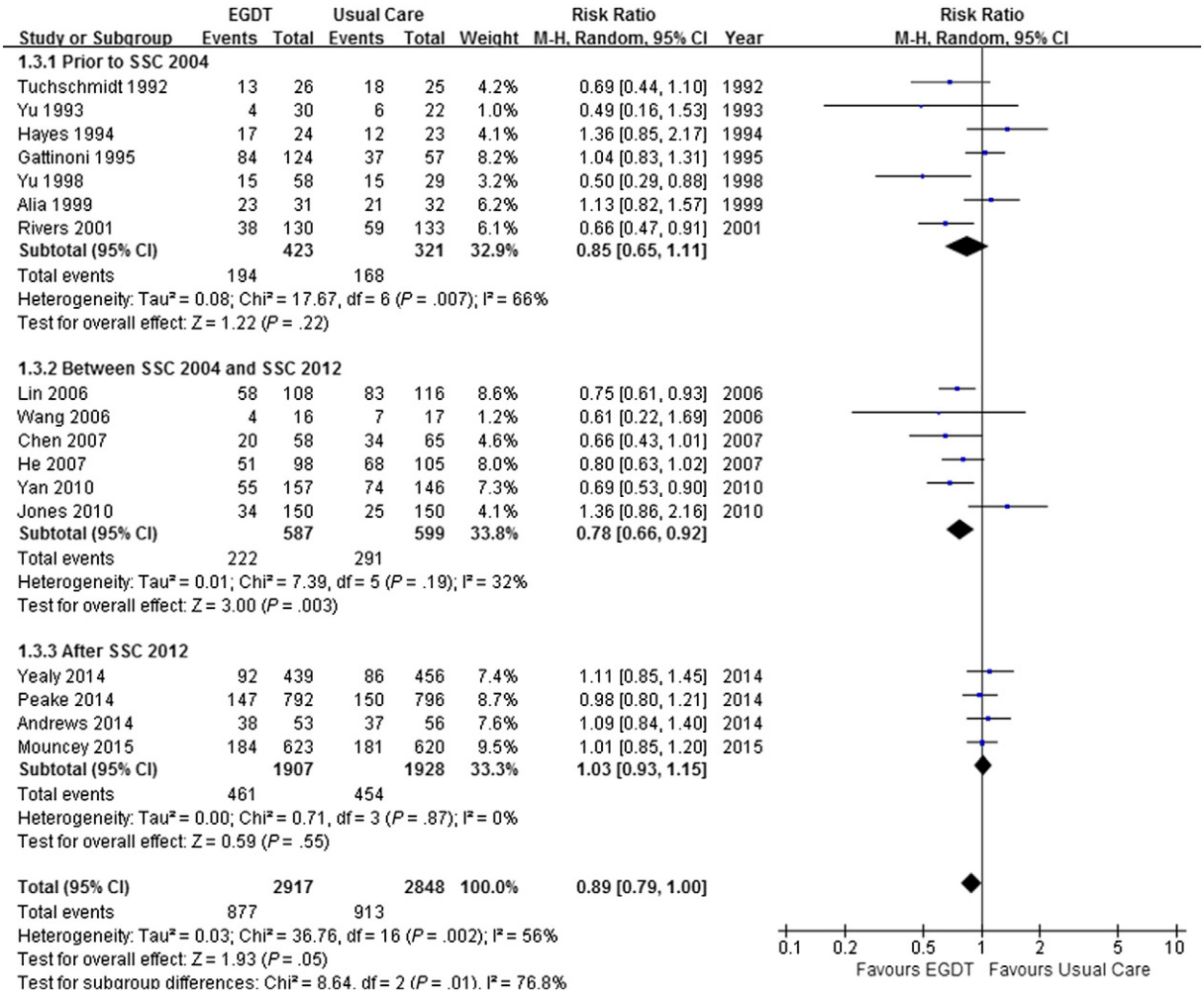

Fig. 4. Effect of EGDT in protocol and usual care groups on mortality rate, grouped by publication years of SSC guidelines. M-H, Mantel–Haenszel.

large trials seem not to suggest a failure of resuscitation bundles including EGDT.

4.1. Improvement of usual care and decreased sepsis mortality

Our subgroup analysis showed that EGDT imparts mortality benefit only when the mortality rate of usual care was above 30%. Mortality rates higher than 30% in usual care for severe sepsis or septic shock are now uncommon in current clinical practice. Recent studies reported decreased sepsis mortality over the past decade [49] and a decline in sepsis mortality from 35.0% to 18.4% between 2000 and 2012 in Australia and New Zealand [50]. A recent investigation reported the septic shock–associated crude mortality was 46.5% [51], and 19% to 29% mortalities reported in recent trios were far from this crude mortality pooled from 44 studies reporting septic shock–associated mortality [13-15]. This reference mortality of 46.5% is exactly identical to that of control group in the original EGDT trial and was reported by one of the same author of the ProCESS trial. This mortality was a major criticism of the EGDT trial. This mortality represents confirmation of the external validity of the original EGDT trial. More importantly, it supports the premise that sepsis mortality has dropped from 46.5% to less than 30% since the introduction of EGDT.

The recent marked decline in the mortality of septic shock can be attributed to the integration of the SSC resuscitation bundles into our daily bedside practices. Bundle compliance has been associated with increased survival [11,19]. Based on the reported volumes of fluids administered before randomization in the ProCESS, ARISE, and ProMISe trials, usual care appears to now include these early interventions and has evolved to be consistent with published protocols [14,15]. Recent literatures demonstrated that a reduction in reported hospital mortality rates was associated with SSC participation [25,52-54]. In a previous 7.5-year observational study showed that increased compliance with the SSC performance bundles was associated with a 25% RR reduction in mortality rate [55]. They reported that an overall lower mortality rate of 29.0% was observed in high-compliance sites, compared with 38.6% in low-compliance sites. Our cutoff of 30% mortality may reflect high compliance to SSC bundles. With the ubiquitous changes in sepsis care over the last 15 years, it would be now difficult to conduct another trial of protocolized care with adequate control group.

4.2. Surviving Sepsis Campaign publication years and decreased sepsis mortality

Comparison of mortality rates according to the publication years of the SSC guidelines revealed a consistent mortality benefit only between 2004 and 2012, with low heterogeneity. This period is after the first SSC guidelines were published in 2004 [5] and before the second updated SSC guidelines were published in 2013 [7]. The EGDT during the first 6 hours of resuscitation was introduced in the first SSC guidelines in 2004 as a grade B recommendation [5]. The same EGDT that included hemodynamic goals for central venous pressure, mean arterial pressure, and central venous oxygen concentration was introduced as grade 1C recommendation in the SSC 2008 and 2012 guidelines [6,7]. The mortality benefit was not seen before the publication of the 2004 SSC

guidelines, with substantial heterogeneity, and after publication of the 2012 SSC guidelines, with no heterogeneity. Therefore, the different impact of EGDT on mortality benefit before and after SSC 2004 guidelines may be associated with improved compliance with EGDT in clinical practices after publication of SSC 2004 guidelines. According to a previous study that assessed the association between SSC bundles compliance and mortality, resuscitation compliance increased over the entire 7.5 years of study period from 2005 through 2012 [55]. Since the first publication of the SSC guidelines in 2004, the compliance may have increased and become integrated into a daily routine before 3 large RCTs were performed [13-15]. As a consequence, mortality benefit from EGDT algorithm proposed by Rivers et al could not be reproduced in recent trios published in 2014 and 2015 [13-15]. The heterogeneity in mortality before the publication of SSC 2004 may be due to institution-specific differences in level of usual care and the quality of the RCTs.

4.3. Review of previous meta-analyses

To our literature review, 8 meta-analyses have been published before 3 recent large trials, most of which reported the significant survival benefits of EGDT [11,18-22,25,28] (Supplemental Table 2). Thereafter, 8 meta-analyses including all the 3 recent large trials have been published, which included different number of studies for different methodologies [23,24,26,27,29-31,56]. Among them, 5 reported no survival benefit of EGDT [23,26,29,31,56], whereas other 3 studies showed significant mortality benefit [24,27,30]. Although the results of meta-analyses were discordant according to different study inclusions, even those meta-analyses reporting no survival benefit of EGDT discussed that the negative results does not mean that EGDT is useless and may be due to improvement of usual care [26,29,31]. The significant heterogeneity of the RCT results reflects potential confounding factors including different compliance rates of resuscitation bundles [26,28,31].

Angus et al [23] included 11 studies and concluded that EGDT does not show improved survival compared with usual care. Rusconi et al [26] included 5 studies and showed that inhospital and 60-day mortality did not differ between EGDT and usual care groups. However, they did not explain the cause of heterogeneity between trials and concluded that heterogeneity precludes a definitive conclusion on the utility of EGDT. Most of these studies did not account for the lack of blinding as a source of bias.

4.4. Illness severity heterogeneity as potential sources of bias

Methodological issues between the recent trios and original EGDT study were compared in Table 1. Yu et al [31] summarized potential sources of bias in terms of illness severity heterogeneity and methodological differences between the original EGDT study and recent trios [13-15]. Blood lactate levels were higher at baseline and $Scvo_2$ levels were lower in the study by Rivers et al compared with those of trios [31]. Patients with acute pulmonary edema were excluded and the incidence of mechanical ventilation was much lower in the trios than the original EGDT study [4]. The patients with septic shock on mechanical ventilation are associated with higher mortality [57]. In addition, incidences of sudden cardiopulmonary decompensation were diminished by 50% as a result of screening in the original EGDT study, which was not mentioned in the trios [58]. These suggest that illness severity was different between original EGDT study and trios, and indicate that the patients of the original EGDT study had higher mortality [59].

4.5. Methodological issues as potential sources of bias

In addition to illness severity, differences in study protocol of trios compared with that of Rivers et al should be addressed as potential confounders. The trio trials were not blinded to the ICU clinicians, whereas care was blinded to the ICU clinicians in the original EGDT study [31,59].

Table 1
Comparison of methodological issues between the recent trios and original EGDT study

	The trios of EGDT trials	Original EGDT study
(1) Illness severity heterogeneity		
Fluid challenge before enrollment	1 L or surrogate	20-30 mL/kg
Blood lactate level at baseline, mg/dL	38-46	62
Baseline $Scvo_2$ levels (0-6 h, %)	75.9 (ARISE trial)	66
Comorbidities	Younger patients with fewer comorbidities	More comorbidities with cardiovascular, hepatic, neurologic, and renal failure
Mechanical ventilation 0-6 h, %	26%	54%
Acute pulmonary edema	Excluded	Included
(2) Study protocol differences		
Blindness	Unblinded to the ICU personnel	ICU personnel were blinded to the group assignment in the ED (double-blinded)
Trial conduct	Length of ED stay <3 h Most of care of the study provided in ICU	Performed only in ED (6-8 h)
Study power	A reduction in sample size after interim analysis (underpowered)	-
Central venous catheterization in the control group	50.9%-61.9% (usual care)	100% (standard therapy)
Corticosteroid use	8%-37%	None
Antibiotics treatment	Before enrollment	After enrollment
(3) Circumstances in which the trials were undergoing		
Time of trial	7-8 years after original EGDT trial (2008-2015), After publication of SSC guidelines	When there was no available sepsis protocols
Sepsis management bundle available in the usual care	Lung protective strategies, Conservative fluid management Glucose control	No protective lung or fluid management strategies No glucose control
Parallel initiatives	Parallel initiatives in the ProMISe trial, ongoing sepsis initiatives in Wales	No
National limits on ED length of stay	Present in Australia, UK	No

ED indicates emergency department

Furthermore, the use of lactate and $Scvo_2$ was not present in the care of patients after the study period. This may lead to performance bias. Other differences in study protocol of trios compared with that of Rivers et al include glucose control, steroid therapy, protective lung strategies, and conservative fluid management strategies. These are components of sepsis management bundle to be completed within 24 hours of admission and may have been incorporated into usual care [5]. Recent reviews [59,60] pointed out that intravenous fluid administration was not different between EGDT and control group in recent trios, whereas the study of Rivers et al [4] showed significant differences. Interestingly, all studies gave similar amounts of fluid when one includes prerandomization fluid with study fluid therapy. These differences may bias the results and diminish the treatment effect of EGDT.

4.6. Circumstances in which the trials were undergoing

Other sources of bias from the circumstances in which the trio trials were undergoing need to be discussed. Most sites in the ProCESS trial had preexisting sepsis protocols (containing EGDT) accessible online before and during enrollment which means that the control group potentially bears significant resemblance to the treatment group. Parallel initiatives in the ProMISe trial (Sepsis Six) and national limits on

emergency department length of stay were in place during these studies' conduction in Australia and United Kingdom [17,61-63]. The baseline mixed venous oxygen saturation was already higher than 70% in ARISE trial, suggesting that oxygen imbalance was not present in most patients. Therefore, in the absence of low $Scvo_2$ values, the scientific question of whether it is of clinical value was not answered. A recent article reviewed an ongoing sepsis initiatives called SEPSIS KILLS pathway during implementation of the ARISE trial in New South Wales [64]. This quality improvement program was associated with a 25% relative mortality reduction. This bias obviously diminishes the treatment effect between groups leading increased probability of a negative trial. This does not mean that EGDT is not effective or debatable.

4.7. Further decrease in mortality

A subset of patients does not respond to the initial resuscitation. These patients with increased illness severity still comprise a significant part of sepsis mortality [14,65]. The current resuscitation bundle of SSC including EGDT may not be able to improve mortality rates in these patients, or recent 3 large RCTs have limited power for evaluating these potentially important subgroups. The EGDT algorithm from Rivers et al can be revised and improved based on recent advances in techniques for monitoring preload and fluid response. Dynamic preload indices including pulse pressure variation and stroke volume variation are now available in mechanically ventilated patients. Portable transthoracic echocardiography can now be applied at bedside and is less invasive and prone to complications than pulmonary artery or central venous oximetry catheters [66]. Even regional and microcirculation can be monitored with new equipment [67,68]. New goal-directed algorithms that take advantage of these technical advances may further decrease mortality rates in patients with severe sepsis.

4.8. Limitations

Our study has several limitations. Firstly, reported mortality outcome variables were not uniform across the studies (Supplemental Table 1) and only 9 trials were assessed as having a low-risk of bias in terms of allocation concealment. Secondly, the effect of regional and center-specific variation in clinical practice cannot be assessed in our trial-level meta-analysis. Thirdly, there is a significant lack of granular data in many of the included studies, which limits the ability of our analysis to make a reliable conclusion. Our result would be nonstatistical because the data is not robust or representative of all the studies.

4.9. Conclusion

In conclusion, our meta-analysis showed that applying EGDT to patients with severe sepsis or septic shock did not impart a significant reduction in mortality over usual care. However, the negative result appears to be due to biases from improvement of usual care and methodological issues. The definition of usual care has evolved in the 15 years because original EGDT trial and most institutions in which recent randomized trials were performed achieved similar levels of short-term mortality in patients receiving usual care to those achieved with EGDT. The methodological issues include lack of blinding by incorporating similar diagnostic and therapeutic interventions as the original EGDT trial. Although the results of 3 recent large trials did not support the systematic use of EGDT over usual care for the management of patients with septic shock, these are caution in this interpretation. This does not mean that EGDT is ineffective; on the contrary, EGDT equally produced the lowest sepsis mortality ever published in the recent trio of trials and showed no harm. The failure of demonstrating a mortality benefit of EGDT in recent trios was due to incorporating elements of EGDT into control group or usual care groups.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.10.019.

Conflict of interest

The authors declared no competing interest.

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