

# BMJ Open Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials

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## ABSTRACT

**Objective:** To determine whether patients with severe sepsis or septic shock could benefit from a strict and early goal-directed therapy (EGDT) protocol recommended by Surviving Sepsis Campaign (SSC) Guidelines.

**Methods:** MEDLINE/PubMed, EMBASE/OVID and Cochrane Central Register of Controlled Trials (CENTRAL) were searched between March 1983 and March 2015. Eligible studies evaluated the outcomes of EGDT versus usual care or standard therapy in patients with severe sepsis or septic shock. The primary outcomes were mortality within 28 days, 60 days and 90 days. Included studies must report at least one metric of mortality.

**Results:** 5 studies that enrolled 4303 patients with 2144 in the EGDT group and 2159 in the control group were included in this meta-analysis. Overall, there were slight decreases of mortality within 28 days, 60 days and 90 days in the random-effect model in patients with severe sepsis or septic shock receiving EGDT resuscitation. However, none of the differences reached statistical significance (RR=0.86; 95% CI 0.69 to 1.06; p=0.16; p for heterogeneity=0.008, I<sup>2</sup>=71%; RR=0.94; 95% CI 0.81 to 1.10; p=0.46; p for heterogeneity=0.16, I<sup>2</sup>=43%; RR=0.98; 95% CI 0.88 to 1.10; p=0.75; p for heterogeneity=0.87, I<sup>2</sup>=0%, respectively).

**Conclusions:** The current meta-analysis pooled data from five RCTs and found no survival benefit of EGDT in patients with sepsis. However, the included trials are not sufficiently homogeneous and potential confounding factors in the negative trials (ProCESS, ARISE and ProMISe) might bias the results and diminish the treatment effect of EGDT. Further well-designed studies should eliminate all potential source of bias to determine if EGDT has a mortality benefit.

## INTRODUCTION

Modern medicine defines sepsis as a deleterious systemic inflammatory response to infection. Sepsis may progress to severe sepsis and septic shock, both of which are life-

## Strengths and limitations of this study

- Early goal-directed therapy (EGDT) was first reported by Rivers *et al* to be of surviving benefit in patients with severe sepsis and septic shock. Though the EGDT protocol is recommended by Surviving Sepsis Campaign (SSC) Guidelines, its therapeutic value remains controversial. The current meta-analysis pooled data from five randomised controlled trials (RCTs) and found no survival benefit of EGDT in patients with sepsis. However, the included trials are not sufficiently homogeneous and potential confounding factors in the negative trials (ProCESS, ARISE and ProMISe) might bias the results and diminish the treatment effect of EGDT. Further well-designed studies should eliminate all potential source of bias to determine if EGDT has a mortality benefit. Our study focusing specifically on high-quality RCTs would provide a timely guide in the management of severe sepsis or septic shock using EGDT so far.
- Our meta-analysis has several limitations. First, the number of studies that met the inclusion criteria for this meta-analysis was relatively small due to the strict implementation of resuscitation goals in the EGDT group according to SSC guidelines. Second, this study did not take all potential confounds into account that may affect the mortality. Lastly, despite the strict inclusion criteria that were applied, a severe degree of heterogeneity cannot be ruled out because of the difference in patient populations, study design and the improved management of the control group over the decade.

threatening health problems affecting millions of people worldwide. Also, sepsis is responsible for huge economic and medical resources consumption.<sup>1–3</sup> Besides urgent measures to treat infections with antimicrobial agents and to eliminate the offending microorganisms, haemodynamic and respiratory supports are important managements for sepsis. Early goal-directed therapy

(EGDT), first reported by Rivers *et al*<sup>4</sup> in 2001, was used to treat patients with severe sepsis and septic shock, which significantly lowered mortality compared with those who were given standard therapy (30.5% vs 46.5%). Though the EGDT protocol is recommended by Surviving Sepsis Campaign (SSC) Guidelines in 2004 (later updated in 2008 and 2012),<sup>1 5 6</sup> it remained to be questioned because of the complexity of resuscitation protocol, potential risks associated with its elements,<sup>7</sup> and concerns about the generalisability of Rivers *et al* findings.<sup>8 9</sup> Furthermore, three large multicentre randomised clinical trials (RCTs) have recently shown the ineffectiveness of EGDT in the initial management of patients with septic shock, which leads to the debatable efficacy of EGDT.<sup>10–12</sup> To better specify the effect of EGDT, we conducted the present meta-analysis focusing on high-quality RCTs only and discussed the effects of a strict EGDT in accordance with SSC Guidelines on mortality.

## METHODS

Since this is a meta-analysis of previously published studies, ethical approval and patient consent are not required.

### Search strategy

This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions statement and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched MEDLINE/PubMed, EMBASE/OVID, Cochrane Central Register of Controlled Trials (CENTRAL) and the System for Information on Grey Literature between March 1983 and March 2015. Our search was restricted to RCTs published in full-text versions; no language restrictions were applied. Our search strategy was based on three search themes, using (1) 'sepsis' or 'severe sepsis' or 'septic shock' or 'septicemia' or 'septicaemia' or 'pyohemia' or 'pyaemia' or 'pyemia'; and (2) 'EGDT' or 'goal directed therapy' or 'early resuscitation' or 'protocol based' or 'early goal directed strategy'; and (3) 'randomised controlled trial' or 'controlled clinical trial' or 'randomised' or 'randomly' or 'trial' or 'groups' (Electronic search strategies are provided in online supplementary appendix 1). A secondary search was performed by manually searching bibliographies and conferences to identify additional relevant studies.

### Selection criteria

Study inclusion criteria were as follows: (1) Design: randomised controlled parallel trials; (2) Population: adult patients (>18 years) with severe sepsis or septic shock. Studies that included patients with sepsis secondary to non-infectious causes were excluded; (3) Intervention: a strict EGDT protocol, defined as a 6 h resuscitation goals in accordance with SSC guidelines including (a)

central venous pressure (CVP) 8–12 mm Hg, (b) mean arterial pressure (MAP)  $\geq 65$  mm Hg, (c) Urine output (UO)  $\geq 0.5$  mL/kg/h, (d) Superior vena cava oxygenation saturation (ScvO<sub>2</sub>) or mixed venous oxygen saturation (SvO<sub>2</sub>)  $\geq 70\%$ ; (4) Control: usual care or standard therapy; (5) Outcomes: mortality, duration of hospital stay, APACHE II score and use of organ support. Eligible studies must report at least one metric of primary outcome, that is, mortality. Secondary outcomes that focused on duration of hospital stay, APACHE II score and use of organ support (cardiovascular, respiratory and renal system) were also analysed since the data were available in at least three trials.

### Data extraction

Three authors independently screened the titles and abstracts of initial search results and extracted data with a standardised data collection form. The following information was extracted from each trial: first author, year of publication, number of patients (EGDT/control), study design, clinical setting, study population, goals of each group (EGDT/control), timing of EGDT and mortality end point. Bin Liu, the senior author, adjudicated any disagreements between the reviewers.

### Validity assessment

We assessed methodological quality using the Cochrane Collaboration risk of bias tool that considered seven different domains: adequacy of sequence generation, allocation concealment, blinding of participants, blinding for outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias.<sup>13</sup>

### Quality of evidence

Quality of evidence was rated by GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system<sup>14</sup> using GRADE profiler V.3.6 software. The GRADE system classifies the quality of evidence in one of four levels: high, moderate, low and very low. Meta-analysis based on RCTs starts as high-quality evidence, but the confidence may be decreased for the following reasons: study limitation, inconsistency of results, indirectness of evidence, imprecision and reporting bias.

### Statistical analysis

For dichotomous data, we estimated the relative risk (RR) with 95% CI to describe the size of treatment effect. For continuous variables, standard mean difference (SMD) was employed.

Homogeneity assumption was tested with I<sup>2</sup> statistics. It is calculated as  $I^2 = 100\% \times (Q - df) / Q$ , where Q is Cochran's heterogeneity statistic.<sup>15</sup> Heterogeneity was suggested if  $p \leq 0.10$ . I<sup>2</sup> values of 0–24.9% indicated no heterogeneity, 25–49.9% mild heterogeneity, 50–74.9% moderate heterogeneity and 75–100% considerable heterogeneity.

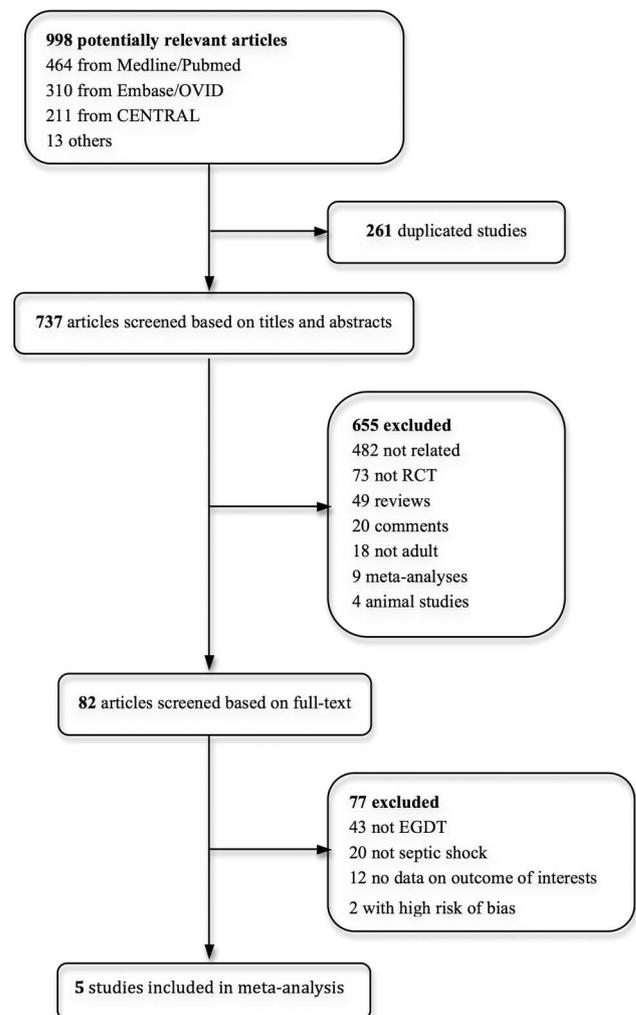
Synthesis of the data was performed using the random effects model. For accurate identification, publication bias was only conducted with data sets of at least 10 data. The publication bias was not assessed on account of the limited number of included studies. Sensitivity analyses were carried out for different subgroups according to a variety of differences in study design.

All analyses were performed using Review Manager (RevMan) (Computer program) V.5.2. Significant differences are set at a two-sided  $p$  value  $<0.05$ .

## RESULTS

### Literature identification and study characteristics

Our search yielded 998 potentially eligible articles (464 from MEDLINE/PubMed, 310 from EMBASE/OVID, 211 from CENTRAL and 13 from other sources). After removing 261 duplicated studies, three independent authors screened 737 articles according to the inclusion criteria. A total of 655 publications were eliminated on the basis of titles or abstracts, and 82 publications were based on full texts. Eventually, five RCTs enrolling 4303 patients, with 2144 in the EGDT group and 2159 in the control group, were included in this meta-analysis (figure 1).<sup>4 10–12 16</sup> The characteristics of the eligible trials are described in table 1. Patients enrolled in all these five studies were adults with severe sepsis or septic shock. EGDT within the first 6 h was conducted in all experimental groups of included trials in accordance with SSC guidelines. Usual care was provided by the treating physician in the control group of the ProCESS (Protocolized care for early septic shock) trial, ProMiSe (Protocolized Management in Sepsis) trial and ARISE (Australasian resuscitation in sepsis evaluation) trial. In addition to the aforementioned, the first one, namely the ProCESS trial, conducted another control group using standard therapy, where the components were less aggressive than those of EGDT. Meanwhile, Rivers *et al* and Yan *et al* treated patients in the control group using standard therapy on the basis of haemodynamic monitoring, which is similar to the EGDT group but lacked ScvO<sub>2</sub>. All these studies were published in English except the study of Yan *et al*, which is in Chinese. The Chinese study was conducted in the intensive care unit (ICU), the Rivers *et al* in the emergency department, while the rest three in the emergency department, ICU or both due to the national limits on length of stay in emergency department. All studies were designed as multicentre trials except that of Rivers *et al*. All publications reported mortality with more than one end point. The assessment of risk of bias is shown in figure 2. Every study described appropriate sequence generation while the allocation concealment and blinding of outcome assessment were unclear in the trial of Yan *et al*. On account of the specialty of the intervention, none of the five trials were able to perform a double-blinded study except that of Rivers *et al*, whose study care was blinded to the ICU clinicians while the rest four were unblinded after the first 6 h resuscitation.



**Figure 1** Study selection. RCT, randomised clinical trial; EGDT, early goal-directed therapy.

### Primary outcome

More than one metric of mortality was provided by each eligible trial. Therefore, we conducted mortality analysis on the basis of different end points including 28-day, 60-day and 90-day mortality. Regarding the two control groups in ProCESS, usual care was included in this meta-analysis as a control group, while a substitute of standard therapy did not change the results of any primary outcomes. As shown in figure 3, five studies reported the incidence of death in 28 days except the ProCESS trial, which provided it in 30 days. The 28-day death had occurred in 442 of 2143 patients (20.6%) in the EGDT group and in 487 of 2153 patients (22.62%) in the control group. The 2.0% mortality decrease did not reach statistical significance (RR=0.86; 95% CI 0.69 to 1.06;  $p=0.16$ ;  $p$  for heterogeneity=0.008,  $I^2=71%$ ; figure 3). The 60-day mortality reported in four trials tended to be lower in the EGDT group (22.7% (450 of 1986 patients) vs 23.5% (473 of 2011 patients)), but this did not reach statistical significance (RR=0.94; 95% CI 0.81 to 1.10;  $p=0.46$ ;  $p$  for heterogeneity=0.16,  $I^2=43%$ ;

**Table 1** Characteristics of included randomised controlled trials

Source	Number of patients (EGDT/control)	Design	Clinical setting	Study population	Goals in EGDT group	Goals in control group	Timing of EGDT	Mortality end point
Rivers <i>et al</i> 2001	263 (130/133)	P-R-NB-SC	ED	Adult patients with severe sepsis, septic shock or sepsis syndrome	SvO <sub>2</sub> ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Standard therapy: CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Within the first 6 h	Hospital 28-day 60-day
Yan <i>et al</i> 2010	303 (157/146)	P-R-NB-MC	ICU	Adult patients with severe sepsis or septic shock	ScvO <sub>2</sub> ≥70% CVP:8–12 mm Hg SBP >90 mm Hg MAP ≥65 mm Hg UO ≥0.5 mL/kg/h	Standard therapy: CVP:8–12 mm Hg SBP >90 mm Hg MAP ≥65 mm Hg UO ≥0.5 mL/kg/h	Within the first 6 h	ICU 28-day
ProCESS 2014	895 (439/456) 885 (439/446)	P-R-NB-MC	ED/ICU	Adult patients with septic shock	ScvO <sub>2</sub> ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Usual care Standard therapy: SBP ≥100 mm Hg	Within the first 6 h	30-day 60-day 90-day
ARISE 2014	1591 (793/798)	P-R-NB-MC	ED/ICU	Adult patients with septic shock	ScvO <sub>2</sub> ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Usual care	Within the first 6 h	ICU Hospital 28-day 60-day 90-day
ProMISe 2015	1251 (625/626)	P-R-MB-MC	ED/ICU	Adult patients with septic shock	ScvO <sub>2</sub> ≥70% CVP ≥8 mm Hg MAP >60 mm Hg SBP >90 mm Hg	Usual care	Within the first 6 h	Hospital discharge 28-day 60-day 90-day

CVP, central venous pressure; ED, emergency department; EGDT, early goal-directed therapy; ICU, intensive care unit; MAP, mean arterial pressure; MC, multicentre; NB, non-blinded; P, prospective; R, randomised; SBP, systolic blood pressure; SC, single centre; ScvO<sub>2</sub>, central venous oxygen saturation; SvO<sub>2</sub>, mixed venous oxygen saturation; UO, urine output.

Study	ARISE2014	ProCESS2014	ProMISe2015	Rivers2001	Yan2010	
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)	+	+	+	+	+	
Other bias	+	+	+	+	+	

**Figure 2** The assessment of risk bias.

figure 3).<sup>4 10–12</sup> Only three of the five studies conducted a follow-up as long as 90 days.<sup>10–12</sup> EGDT was associated with decreased 90-day mortality (25.3% (460 of 1820 patients) vs 25.7% (470 of 1828 patients)), although the difference did not reach statistical significance (RR=0.98; 95% CI 0.88 to 1.10; p=0.87; p for heterogeneity=0.87, I<sup>2</sup>=0%; figure 3).

#### 28-day mortality

Study or Subgroup	EGDT		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
ARISE2014	117	792	127	797	21.6%	0.93 [0.74, 1.17]	
ProCESS2014	91	439	85	456	20.1%	1.11 [0.85, 1.45]	
ProMISe2015	155	625	152	621	23.3%	1.01 [0.83, 1.23]	
Rivers2001	40	130	61	133	17.8%	0.67 [0.49, 0.92]	
Yan2010	39	157	62	146	17.2%	0.58 [0.42, 0.81]	
<b>Total (95% CI)</b>		<b>2143</b>		<b>2153</b>	<b>100.0%</b>	<b>0.86 [0.69, 1.06]</b>	
Total events	442		487				
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 13.78, df = 4 (P = 0.008); I <sup>2</sup> = 71%							
Test for overall effect: Z = 1.41 (P = 0.16)							

#### 60-day mortality

Study or Subgroup	EGDT		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
ARISE2014	132	792	139	796	26.4%	0.95 [0.77, 1.19]	
ProCESS2014	92	439	86	456	20.9%	1.11 [0.85, 1.45]	
ProMISe2015	176	625	178	626	32.5%	0.99 [0.83, 1.18]	
Rivers2001	50	130	70	133	20.2%	0.73 [0.56, 0.96]	
<b>Total (95% CI)</b>		<b>1986</b>		<b>2011</b>	<b>100.0%</b>	<b>0.94 [0.81, 1.10]</b>	
Total events	450		473				
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 5.23, df = 3 (P = 0.16); I <sup>2</sup> = 43%							
Test for overall effect: Z = 0.74 (P = 0.46)							

#### 90-day mortality

Study or Subgroup	EGDT		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
ARISE2014	147	792	150	796	28.5%	0.98 [0.80, 1.21]	
ProCESS2014	129	405	139	412	31.1%	0.94 [0.78, 1.15]	
ProMISe2015	184	623	181	620	40.4%	1.01 [0.85, 1.20]	
<b>Total (95% CI)</b>		<b>1820</b>		<b>1828</b>	<b>100.0%</b>	<b>0.98 [0.88, 1.10]</b>	
Total events	460		470				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.27, df = 2 (P = 0.87); I <sup>2</sup> = 0%							
Test for overall effect: Z = 0.31 (P = 0.75)							

**Figure 3** Forest plot for the 28-day, 60-day and 90-day mortality. A pooled RR was calculated using the random effects model according to the Mantel-Haenszel (M-H) method. EGDT decreased 28-day, 60-day and 90-day mortality but with no statistical significance. EGDT, early goal-directed therapy.

#### Secondary outcome

The length of hospital stay<sup>4 11 16</sup> (SMD=-0.11; 95% CI -0.31 to 0.10; p=0.31; p for heterogeneity=0.04, I<sup>2</sup>=69%) and APACHE II score<sup>4 11 16</sup> (SMD=-0.29; 95% CI -0.64 to 0.06; p=0.11; p for heterogeneity<0.0001, I<sup>2</sup>=89%) did not differ significantly between the two groups. Also, receipt of advanced cardiovascular,<sup>4 10–12</sup> respiratory<sup>4 10–12</sup> or renal<sup>10–12</sup> support was equivalent between two groups. (RR=1.08; 95% CI 0.95 to 1.22; p=0.24; p for heterogeneity=0.009, I<sup>2</sup>=74%, RR=1.04; 95% CI 0.92 to 1.17; p=0.57; p for heterogeneity=0.21, I<sup>2</sup>=36% and RR=1.03; 95% CI 0.86 to 1.24; p=0.74; p for heterogeneity=0.88, I<sup>2</sup>=0%, respectively).

#### Sensitivity analyses

Sensitivity analysis was performed according to a variety of differences in study design (see online supplementary appendix 2). There was no significant decrease in 28-day mortality when excluding the single-centre trial.<sup>4</sup> No significant decrease of in-hospital mortality was observed by pooling the death data in patients with septic shock.<sup>4 10–12</sup> Both usual-care therapy and standard

therapy showed a comparable mortality to EGDT therapy.

### Quality of evidence

GRADE system grades of evidence are very low for 28-day mortality, and moderate for 60-day mortality and 90-day mortality (see online supplementary appendix 3).

### DISCUSSION

The main finding of this meta-analysis is that a strict EGDT protocol conducted in accordance with SSC guidelines showed equivalent survival benefits in patients with severe sepsis or septic shock. Meanwhile, the length of hospital stay, APACHE II score and receipts of advanced cardiovascular, respiratory or renal support did not differ significantly between EGDT and other protocols.

Severe sepsis or septic shock is associated with sepsis-induced (persisting) tissue hypoperfusion and disrupted balance of tissue oxygen use.<sup>3</sup> An effective initial fluid resuscitation is relied on to prevent the haemodynamic collapse and ongoing of organ failure.<sup>1</sup> The prespecified MAP, CVP and ScvO<sub>2</sub> goals are recommended in the EGDT protocol to adjust intravenous fluids, vasopressors, inotropes and blood transfusions. CVP and MAP reflect the intravascular volume status and organ perfusion, and could direct the administration of fluid and vasoactive drugs.<sup>17 18</sup> Moreover, a goal of maintaining ScvO<sub>2</sub> ≥ 70% could restore a balance between oxygen delivery and oxygen demand,<sup>1 5 6</sup> and normoxia was associated with decreased mortality in patients with sepsis as reported by Pope *et al*.<sup>19</sup> Also, previous meta-analyses of observational studies<sup>20–22</sup> or

clinical trials<sup>23</sup> reported that EGDT or a 6 h sepsis bundle including EGDT significantly reduces mortality in patients with sepsis over the past decade.

The current meta-analysis pooled data from all well-designed RCTs and focused on whether a strict EGDT protocol combining all goals (four indicators, ie, MAP, CVP, UO, ScvO<sub>2</sub>/SvO<sub>2</sub>) was necessary to achieve survival benefit in patients with sepsis. While the findings were consistent with the three recent negative trials,<sup>10–12</sup> they contradicted those of previous meta-analyses.<sup>20–23</sup> Owing to the strict selection criteria in this meta-analysis, only five RCTs were included eventually. Although all of them are all well-designed RCTs, they are not sufficiently homogeneous in terms of patient population and methodology (table 2). First, the study cohorts between these trio of trials and Rivers *et al* were of different illness severity. The patients of Rivers *et al* were slightly older than those in the three recent studies. Also, higher rates of chronic coexisting health condition, higher initial serum lactate levels and lower ScvO<sub>2</sub> levels were found in the population of Rivers *et al*'s study, and the APACHE II score and mechanical ventilation rates were relatively lower in the three recent trials.<sup>10–12</sup> Besides, the fluid challenge of in Rivers *et al* was much more than that of the three trials (20 to 30 mL per kilogram of body weight vs 1000 mL), which yields a haemodynamic heterogeneity in these enrolled studies. Second, there are some methodological differences that should be examined before viewing the results. In Rivers *et al*'s study, patient care was blinded to the ICU clinicians while the rest of the trials were unblinded. Corticosteroid was administrated in 8–37% of patients in the trio of trials, but not in that of Rivers *et al*, which might be associated with

**Table 2** The source of bias in terms of patient population and methodology of included trials

	Rivers <i>et al</i>	ProCESS, ARISE and ProMISe
Illness severity heterogeneity*		
Fluid challenge before enrolment	20 to 30 mL/kg	1000 mL
Blood lactate levels at baseline, mmol/L	6.9	4.2–5.1
APACHE II score at baseline	20.4	15.8–20.7
ScvO <sub>2</sub> , at baseline, %	49.2	NR
ScvO <sub>2</sub> , 0–6 h, %	66	75.9†
Mechanical ventilation 0–6 h, %	53.8	19.0–22.4
28-day mortality	49.2%	15.9–24.5%
Methodological differences		
CVC, %‡	100	50.9–61.9
Corticosteroid use	None	8–37%
Antibiotics treatment	After enrolment	Before enrolment
Treatment in control group	Well-defined	Vague
Blinding	Double blinded	Unblinded to the ICU clinicians
Time of conduction	1997–2000	2008–2014 (EGDT recommendation in SSC Guidelines and the sepsis six)

\*The data in control groups.

†The data in the EGDT group in ARISE.

‡The central venous catheterisation in control group: standard therapy in Rivers *et al* and usual care in the trio of trials.

CVC, central venous catheterisation; EGDT, early goal-directed therapy; NR, not reported; ScvO<sub>2</sub>, central venous oxygen saturation; SSC, Surviving Sepsis Campaign.

improved mortality in the recent three trials, as it was reported that corticosteroid therapy showed a significant shock reversal effect and improved mortality in vasopressor-unresponsive patients with septic shock.<sup>24–26</sup> Third, the recent three trials did not compare the causes of death between two groups, especially the rate of death due to sudden cardiovascular collapse. Rivers *et al*<sup>4</sup> assumed that sudden cardiovascular collapse was an important cause of early death and that the EGDT benefits arose from early identification of cardiovascular collapse. Importantly, the mortality in all groups of the recent three trials was much lower than that in Rivers *et al*'s study. The significantly lower mortality may be the result of rapid recognition and management of patients with severe sepsis, and the aggressive intravenous fluids and antibiotics treatment prior to enrolment in these studies. Therefore, on the basis of these biases, it is inappropriate to conclude that EGDT is a useless protocol.

It is worth mentioning that the treatments made by the treating clinical team in the usual care group were not well defined in the trio of trials, and the control groups and treatment groups were not received distinctly different treatments in a blinded fashion, which may cause a crossover of treatment between the two groups. Also, it is rational to assume that the usual care has changed dramatically due to the influence of Rivers *et al*'s trial advocating EGDT. It is evidenced by the progressive decrease in sepsis mortality over the past decade.<sup>27</sup> Also, the trio of trials were conducted with a duration ranging between 4 and 8 years, during which period the SSC Guidelines recommending the EGDT protocol updated in 2008 (later updated in 2012) and the UK used a sepsis six protocol before and during the ProMISE trial conduction.<sup>28–29</sup> What is more important is that even in the usual care group, the central venous catheterisation (a fundamental component of the EGDT) rates were over 50%, and MAP and CVP targets were achieved within the initial resuscitation in the three recent trials.<sup>10–12</sup> Hence, the crossover of treatment between the two groups and rapid and effective resuscitation in management of patients with sepsis with modified clinician behaviours in the usual care group might render the effect of EGDT underpowered.<sup>30–31</sup>

Owing to a lack of high-level evidence of validation of EGDT replicating Rivers *et al*'s trial, the trio of trials designed multicentre RCTs. However, potential confounding of recruiting milder patients, more aggressive antibiotic therapy and crossover of treatments between the control groups and the EGDT groups due to unblinding might bias the results and diminish the treatment effect of EGDT. Further well-designed studies should eliminate all potential source of bias mentioned above to determine if EGDT has a mortality benefit. Indeed, the results of current meta-analysis and recent trials did not undermine the effect of EGDT; instead, they urged us to find a more practical and cost-saving

approach that could yield similar survival outcomes. Lin *et al*<sup>32</sup> employed a modified EGDT protocol without the monitoring of ScvO<sub>2</sub> and found a decrease in mortality. A clinical trial confirmed that the value of lactate clearance is equivalent to ScvO<sub>2</sub> using the EGDT algorithm.<sup>33</sup> Moreover, some new researches are on the way, aiming to use a minimally invasive protocol utilising oesophageal Doppler monitoring (EDM) to replace continuous ScvO<sub>2</sub> (NCT00535821).

Our meta-analysis has several limitations. First, the number of studies that met the inclusion criteria for this meta-analysis was relatively small due to the strict implementation of resuscitation goals in the EGDT group according to SSC guidelines. Consequently, subanalyses that could be conducted to compare EGDT with different control groups were limited. Second, end points of the mortality in each trial ranged from 28 days to 90 days, which may have a potential effect on overall mortality. However, we conducted mortality analysis according to different end points including mortality in 28 days, 60 days and 90 days, and the results were consistent. Third, this study did not take all potential confounds (eg, age, chronic coexisting health conditions, initial serum lactate levels as well as APACHE II score) into account, which may affect the mortality. Lastly, despite the strict inclusion criteria that were applied, a severe degree of heterogeneity cannot be ruled out because of the difference in patient populations, study design and the improved management of the control group over the decade.

## CONCLUSIONS

The current meta-analysis pooled data from five RCTs and found no survival benefit of EGDT in patients with sepsis. However, the included trials are not sufficiently homogeneous and potential confounding factors in the negative trials (ProCESS, ARISE and ProMISE) might bias the results and diminish the treatment effect of EGDT. Further well-designed studies should eliminate all potential sources of bias to determine if EGDT has a mortality benefit.

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