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A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

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For the ARISE, ProCESS, ProMISe and PRISM Investigators.

Take-home message: EGDTfor patients presenting to the ED with early septic shock does notdecrease mortality but does increase ICU resource utilisation.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3822-1) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* To determine whether early goal-directed therapy (EGDT) reduces mortality compared with other resuscitation strategies for patients presenting to the emergency department (ED) with septic shock. *Methods:* Using a search strategy of PubMed, EmBase and CENTRAL, we selected all relevant randomised clinical trials published from January 2000 to January 2015. We translated non-English papers and contacted authors as necessary. Our primary analysis generated a pooled odds ratio (OR) from a fixed-effect model. Sensitivity analyses explored the effect of including non-ED studies, adjusting for study quality, and conducting a random-effects model. Secondary outcomes included organ support and hospital and ICU length of stay. *Results:* From 2395 initially eligible abstracts, five randomised clinical trials ($n = 4735$ patients) met all criteria and generally scored high for quality except for lack of blinding. There was no effect on the primary mortality outcome (EGDT: 23.2 % [495/2134] versus control: 22.4 % [582/2601]; pooled OR 1.01 [95 % CI 0.88–1.16], $P = 0.9$, with heterogeneity [$I^2 = 57$ %; $P = 0.055$]). The pooled estimate of 90-day mortality from the three recent multicentre studies ($n = 4063$) also showed no difference [pooled OR 0.99 (95 % CI 0.86–1.15), $P = 0.93$] with no heterogeneity ($I^2 = 0.0$ %; $P = 0.97$). EGDT increased vasopressor use (OR 1.25 [95 % CI 1.10–1.41]; $P < 0.001$) and ICU admission [OR 2.19 (95 % CI 1.82–2.65); $P < 0.001$]. Including six non-ED randomised trials increased heterogeneity ($I^2 = 71$ %; $P < 0.001$) but did not change overall results [pooled OR 0.94 (95 % CI 0.82 to 1.07); $P = 0.33$]. *Conclusion:* EGDT is not superior to usual care for ED patients with septic shock but is associated with increased utilisation of ICU resources.

Keywords Early goal-directed therapy or EGDT · Resuscitation · Septic shock · Central venous oxygen saturation · Meta-analysis · Systematic review · Randomised clinical trials

Introduction

In 2001, Rivers and colleagues published a single-centre, randomised trial of protocolised resuscitation for patients presenting to the emergency department (ED) with septic shock [1]. The therapies prescribed in this specific, 6-h resuscitation algorithm, termed early goal-directed therapy (EGDT), were guided by the optimisation of haemodynamic goals targeting both arterial and central venous pressure and a central venous oxygenation saturation ($ScvO_2$) of 70 % or greater. EGDT decreased short-term mortality compared with non-protocolised standard resuscitation. A number of non-randomised, predominantly before–after, studies subsequently reported a survival benefit with EGDT, even when implementation was incomplete [2–4]. Since 2004, the Surviving Sepsis Campaign guidelines have endorsed EGDT [5] but the uptake of this resuscitation approach has been variable [6]. Barriers to uptake include concerns regarding the generalisability of the original EGDT trial findings outside of a single US centre, the potential risks associated with individual elements of the protocol and the infrastructure and resource requirements needed to implement EGDT. Three recent large, multicentre, randomised clinical trials conducted in the USA [7, 8], Australasia [9, 10] and the UK [11, 12] failed to find that EGDT decreased mortality.

We sought to systematically review the randomised clinical trial evidence for EGDT in the resuscitation of

patients presenting to the ED with septic shock and to address the primary question of whether EGDT, compared with other resuscitation strategies, is associated with a survival benefit. Our secondary objective was to evaluate EGDT in all patients with septic shock irrespective of presenting source or timing.

Methods

We prospectively registered our study protocol with PROSPERO (International prospective register of systematic reviews; CRD2014015682). The research question was formulated according to the Participants, Interventions, Comparisons and Outcomes (PICO) model: P, patients presenting to the emergency department with septic shock; I, EGDT; C, non-EGDT haemodynamic resuscitation strategy; O, mortality [13]. The methods for reporting the subsequent results have followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14].

Inclusion criteria

We included randomised clinical trials conducted in adult or paediatric patient populations with septic shock that compared EGDT with either usual care or another resuscitation strategy that did not incorporate EGDT. The definition of EGDT was based on the original publication by Rivers et al. [1] as the protocolised administration of intravenous fluids, vasoactive agents and red cell transfusion to achieve the predetermined haemodynamic goals of central venous pressure, mean arterial pressure and $ScvO_2$. We only analysed studies that reported mortality, excluding those reporting only physiological end-points, solely descriptive or non-randomised and any studies published before 2000.

Search strategy

Two authors (SLP, ADe) independently conducted the search of PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for the period 1 January 2000 to 15 January 2015 to identify all randomised clinical trials of EGDT in human subjects with septic shock. The search terms were "sepsis", "septicaemia", "shock, septic", "early goal-directed therapy", "EGDT", "sepsis protocol", "clinical protocols", "central venous oxygen saturation", "$ScvO_2$", "goal-directed resuscitation, goal-directed therapy" combined with sensitive filters to identify randomised clinical trials. There were no language restrictions. The detailed search strategy is reported in the Supplementary Appendix. We also searched clinical trials registries and contacted experts in the field to identify unpublished studies.

Two authors (SLP, ADe) independently reviewed the titles and abstracts of all articles generated by the search to identify potentially relevant studies. We retrieved full-text manuscripts of potentially relevant studies for further evaluation and inclusion if the predefined inclusion criteria were met. We also screened the reference lists of included articles and previous systematic reviews for the same period [15–17] to identify other potentially eligible studies. If needed, we contacted authors to clarify details of trials. Differences of opinion were resolved via discussion and consensus.

Data extraction

Two authors (SLP, ADe) independently extracted predefined data from included studies into standardised data abstraction forms except for articles written in Chinese, which were translated (by C-RC) and data extracted (C-RC, SLP) separately. Information included (1) study characteristics (lead author, publication year, country or region, number of participating sites, number of patients enrolled, ED and/or non-ED source, EGDT and control resuscitation goals); (2) participant characteristics (age, sex, baseline APACHE II score, presence of hypotension and hyperlactataemia); (3) interventions delivered up to 6 h post-randomisation (including intravenous fluids, vasopressors, dobutamine and red cell transfusion); (4) time to antimicrobial administration; (5) receipt and duration of organ support (invasive mechanical ventilation, vasopressors and renal replacement therapy); and (6) outcome (mortality, intensive care unit (ICU) admission and duration of ICU and hospital stay).

Quality assessment

We assessed the quality of the included studies using two independent assessors who had no role in the design, conduct, analysis or reporting of any of the included studies (TI, ADa). The Cochrane Collaboration tool was used to assess the risk of bias for the individual 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 [18]. The risk of bias for each domain was assessed as "high", "low" or "unclear". When differences in assessment

existed, consensus was obtained via discussion between the assessors.

Outcome measures

We classified studies according to the patient entry source, into those conducted among patients presenting to the ED, and those in which some or all the patients enrolled were from the general ward and/or ICU or the source was unable to be determined from either the published article or from attempts to contact the corresponding author of the study.

For the primary objective, the prespecified primary outcome was mortality in studies conducted in patients presenting to the ED with septic shock. If mortality at more than one time was reported for a given trial, we used the mortality identified as the primary outcome for that study in the analysis of our primary objective. We also conducted additional analyses for mortality at 28 days, 90 days and at hospital discharge for studies reporting these mortality outcomes. Secondary outcomes were ICU admission rate and duration of stay in ICU and hospital. Our secondary objective was to assess mortality at any time in patients with septic shock irrespective of presenting source. Mortality was the primary mortality outcome for each study included in the analysis.

Statistical analysis

We used a fixed-effect model to obtain an estimate of the effect size for the primary objective expressed as a pooled odds ratio (OR) with 95 % confidence interval (CI) and presented as a forest plot. We also conducted a sensitivity analysis using a random-effects model. We used univariate meta-regression to assess the effect of each domain of the quality assessment on the overall estimate of treatment effect, as well as other potential sources of heterogeneity. To assess heterogeneity in treatment effect across studies, we used the I^2 statistic. A priori explanations for heterogeneity included (1) methodological quality of the studies (using individual risk of bias domains); (2) harmonised studies (Australasian Resuscitation in Sepsis Evaluation [ARISE], Protocolized Care for Early Septic Shock [ProCESS] and Protocolised Management In Sepsis [ProMISe]) versus non-harmonised studies; (3) control intervention (usual care versus another resuscitation protocol); (4) duration of intervention; and (5) adult versus paediatric populations. Examination of small study effects was conducted by construction and visual examination of funnel plots and Egger's statistic.

To assess the effect of EGDT on receipt and duration of organ support and secondary outcomes (ICU admission and duration of stay in ICU and hospital), we used a fixed-

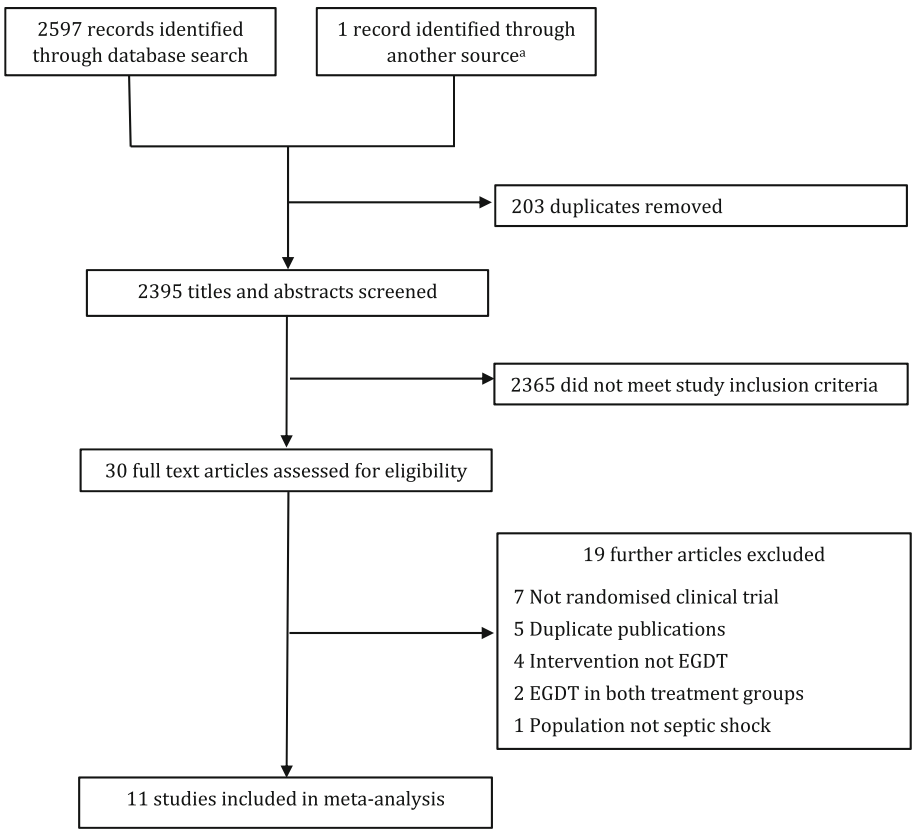

Fig. 1 Study selection EGDT denotes early goal-directed therapy. Identified through personal contact with investigators prior to publication [12][a]

effect model and reported a pooled OR and 95 % CI for categorical variables or overall mean weighted difference (WMD) with 95 % CI for continuous variables. For analysis of our secondary objective (mortality in patients with septic shock irrespective of presenting source), we used the pooled OR with 95 % CI using a fixed-effect model.

We used Stata/SE version 13.1 (StataCorp, College Station, Texas) for analyses and a two-sided *P* value of 0.05 or less to indicate statistical significance.

Results

The preliminary search identified 2598 articles (Fig. 1). After removal of 203 duplicates, we reviewed 2395 abstracts and eliminated 2365 articles not meeting the study inclusion criteria. Two investigators (SLP, ADe) reviewed 30 full-text articles and subsequently excluded 19 as not meeting the inclusion criteria. No trials were excluded because mortality was not reported. Of the 11 remaining studies, five enrolled patients presenting to the ED with septic shock and were suitable for assessment of the primary objective [1, 8, 10, 12, 19]. Of the remaining six studies fulfilling the inclusion criteria for our secondary objective, one enrolled patients presenting to either the ED or recruited in-patients from the general ward or ICU [20] and in five (all published in Chinese), we could not determine the patient source from either the original publication nor following attempts to contact the author using contact details provided in the publication [21–25].

Study characteristics

Table 1 summarises the characteristics of the included studies. Six were conducted in multiple sites and five were single-centre studies. The total number of patients enrolled was 5407, comprising 2459 in the EGDT group and 2948 in the control group. The control was usual care in five studies [1, 10, 12, 21, 22], an alternative resuscitation strategy in five studies [19, 20, 23–25] and in one study both usual care and protocol-based standard therapy [8]. The goals of the alternative resuscitation strategies are described in Table 1. Patient characteristics and therapies delivered during the 6-h resuscitation period are

Table 1 Characteristics of included studies for the primary and secondary objectives

Author	Region	No. of sites	Population	Source	Control(s)	No. of patients	Primary outcome
Primary objective							
Rivers et al. [1]	USA	1	Adult	ED	Usual care	263	In-hospital
Jones et al. [19]	USA	3	Adult	ED	Lactate clearance[c]	300	In-hospital
ProCESS Investigators [8]	USA	31	Adult	ED	Usual care or protocol-based standard therapy[d]	1341	In-hospital[h]
ARISE Investigators [10]	Australasia[a]	51	Adult	ED	Usual care	1600	90-day
ProMISe Investigators [12]	England	56	Adult	ED	Usual care	1260	90-day
Secondary objective							
Wang et al. [21]	China	1	Adult	Unknown[b]	Usual care	33	14-day
De Oliviera et al. [20]	Brazil	2	Paediatric	ED, ward, ICU	ACCM/PALS guidelines[e]	102	28-day
EGDT Collaborative [22]	China	8	Adult	Unknown[b]	Usual care	314	28-day
Tian et al. [23]	China	1	Adult	Unknown[b]	10 or 30 % lactate clearance	71	28-day
Yu et al. [24]	China	1	Adult	Unknown[b]	Lactate clearance ≥10 %[f]	50	28-day
Lu et al. [25]	China	1	Adult	Unknown[b]	PiCCO-guided resuscitation[g]	82	In-hospital

The primary objective included only those studies in which patients presented to the ED with septic shock ($n = 5$). The secondary objective also included those studies in which the presenting source was the ED and the ward or ICU or where the source was not known ($n = 11$)

ProCESS Protocolized Care for Early Septic Shock, *ARISE* Australasian Resuscitation in Sepsis Evaluation, *ProMISe* Protocolised Management In Sepsis, *EGDT* early goal-directed therapy, *ED* emergency department, *ICU* intensive care unit, *ACCM/PALS* The American College of Critical Care Medicine—Paediatric Advances Life Support, *PiCCO* pulse contour continuous cardiac output

[a] ARISE enrolled patients in Australia, New Zealand, Hong Kong, Finland and Republic of Ireland

[b] No response to email communication

[c] Isotonic crystalloids, vasopressors, red cells and dobutamine to achieve central venous pressure ≥8 mmHg, mean arterial pressure ≥65 mmHg and lactate clearance >10 %

[d] Protocol for administration of fluids and vasoactive agents to reach goals for systolic blood pressure and shock index, without requirement for central venous monitoring

[e] Fluids, red cells and vasoactive agents to maintain normal perfusion pressure for age, urine output >1 ml/kg/h, capillary refill <2 s and normal pulses

[f] Fluid resuscitation to maintain central venous pressure ≥8 mmHg, mean arterial pressure ≥65 mmHg and lactate clearance ≥10 %

[g] Fluids and vasoactive agents to maintain an intrathoracic blood volume index of 850–1000 ml/m^2, left ventricular contractile index, stroke volume index and mean arterial pressure of 65 mmHg

[h] In-hospital mortality censored at 60 days

detailed in Tables 2 and 3. Tables S1 and S2 of the Supplementary Appendix detail the receipt and duration of organ support, ICU admission and length of stay in ICU and hospital. The quality assessment of the included studies is shown in Table S3 of the Supplementary Appendix. Given the nature of the intervention, all studies were unblinded and deemed to be at high risk of bias for blinding of participants and personnel. Two studies had a low risk of bias for the remaining domains [10, 12] and nine others were deemed to have additional high or unclear risk for bias in one or more domains.

Patients presenting to the emergency department with septic shock

Mortality

A total of 4735 patients were available for analysis of our primary objective. Overall mortality was 23.2 % (495 of 2134 patients) in the EGDT group and 22.4 % (582 of 2601 patients) in the control group. EGDT did not confer a reduction in overall mortality (pooled OR 1.01 [95 % CI 0.88–1.16]; $P = 0.90$) (Table 4; Fig. 2). There was evidence of heterogeneity ($I^2 = 57$ %; $P = 0.055$). Heterogeneity between studies was not explained by methodological quality, harmonised versus non-harmonised studies or control intervention. There was no variation across the five studies in duration of intervention and all were conducted in adult populations. Sensitivity analysis using a random-effects model did not change the results (Supplementary Appendix Fig. S1). Sensitivity analysis using only usual care as the control and excluding alternative resuscitation strategies (protocol-based standard therapy [8] and lactate clearance [19]) also did not change the results. For the studies reporting 90-day mortality (the three harmonised studies) [8, 10, 12], the pooled OR was 0.99 (95 % CI 0.86–1.15) ($P = 0.93$) with no heterogeneity ($I^2 = 0.0$ %; $P = 0.97$) (Fig. 2). Effect estimates for in-hospital and 28-day mortality also did not demonstrate a reduction in mortality associated with EGDT either using a fixed-effect or random-effects model (Table 4; Supplementary Appendix Figs. S2 and S3 [5].

Organ support and length of hospital and ICU stay

There was no difference in receipt of or duration of organ support other than for receipt of vasopressors which increased with EGDT (OR 1.25 [95 % CI 1.10–1.41]; $P < 0.001$). Post hoc analysis using random-effects

Table 2 Patient characteristics and primary mortality outcome of the included studies

Author	No. of patients		APACHE II score		Hypotension (%)		Lactate (mmol/L)		Primary mortality (%)	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control
Primary objective										
Rivers et al. [1]	130	133	21.4 ± 6.9	20.4 ± 7.4	54.6	51.1	7.7 ± 4.7	6.9 ± 4.5	29.2[f]	44.4[f]
Jones et al. [19]	150	150	NA[b]	NA[b]	82.0	80.1	4.2 ± 3.1	3.9 ± 3.1	22.7	16.7
ProCESS Investigators [8][a]	439	902	20.8 ± 8.1	20.7 ± 7.4	55.6	53.5	4.8 ± 3.1	4.9 ± 3.4	21.0	18.5
ARISE Investigators [10]	796	804	15.4 ± 6.5	15.8 ± 6.5	70.0	69.8	4.4 ± 3.3	4.2 ± 2.8	18.6	18.8
ProMISe Investigators [12]	630	630	18.7 ± 7.1	18.0 ± 7.1	54.1	55.6	5.2 ± 3.5	5.1 ± 3.5	29.5	29.2
Secondary objective										
Wang et al. [21]	16	17	28 ± 7	27 ± 6	100	100	NA	NA	25.0	41.2
De Oliviera et al. [20]	51	51	NA[c]	NA[c]	94.1	92.2	1.1 (0.7–2.5)[e]	1.2 (0.8–2.3)[e]	11.8	39.2
EGDT Collaborative [22]	163	151	23.5 ± 5.7	21.8 ± 6.5	NA	NA	NA	NA	25.2	42.4
Tian et al. [23]	19	43	20.9 ± 8.6	17.6 ± 5.7[d]	100	100	NA	NA	63.2	36.4[d]
Yu et al. [24]	23	25	17.9 ± 3.8	18.2 ± 6.0	100	100	NA	3.4 ± 1.3	28.0	20.0
Lu et al. [25]	40	42	27.6 ± 8.9	28.9 ± 10.1	100	100	7.3 ± 3.1	7.5 ± 3.8	17.5	16.7

Data presented as mean ± SD or percentage (%) unless otherwise indicated. The primary objective included only those studies in which patients presented to the ED with septic shock ($n = 5$). The secondary objective included those studies in which the presenting source was the ED and the ward or ICU or where the source was not known ($n = 11$). The control for analyses was usual care or another non-EGDT resuscitation strategy

ProCESS Protocolized Care for Early Septic Shock, *ARISE* Australasian Resuscitation in Sepsis Evaluation, *ProMISe* Protocolised Management In Sepsis, *EGDT* early goal-directed therapy, *APACHE* Acute Physiology And Chronic Health Evaluation, *NA* not available

[a] Data presented for the control group is usual care and protocol-based standard therapy groups combined. For the usual care and protocol-based standard therapy groups separately, APACHE II score was 20.7 ± 7.5 and 20.6 ± 7.4, respectively; presence of shock, 53.3 and 53.4 %; lactate 4.9 ± 3.1 and 5.0 ± 3.6 mmol/L; and primary mortality 18.6 and 18.2 %

[b] Simplified Acute Physiology Score for the EGDT and control groups was 44.1 ± 17.3 and 44.8 ± 18.4, respectively

[c] Paediatric Risk of Mortality Score (PRISM) (median and interquartile range) for the EGDT and control groups was 7.0 (5–12) and 8.0 (5–12), respectively

[d] Data presented for 10 % lactate clearance group only. APACHE II score and primary mortality for the 30 % lactate clearance group were 18.0 ± 6.8 mmol/L and 28.6 %

[e] Median and interquartile range

[f] Percentages presented are different to those reported in the original publication [1] in which mortality was calculated by the Kaplan–Meier product-limit method

Table 3 Interventions delivered between randomisation and 6 h post-randomisation

Author	Fluids (ml)		Vasopressor (%)		Dobutamine (%)		Blood transfusion (%)		Time to first antimicrobial (min), median (IQR)	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control
Primary objective										
Rivers et al. [1]	4981 ± 2984	3499 ± 2438	27.4	30.3	13.7	0.8	64.1	18.5	NA	NA
Jones et al. [19]	4300 ± 2210	4500 ± 2360	75.3	72.0	5.3	3.3	3.3	7.3	115 (66–170)	115 (62–180)
ProCESS Investigators [8]	2805 ± 1957	2783 ± 1880	54.9	48.1	5.7	1.0	14.4	7.9	NA	NA
ARISE Investigators [10]	1964 ± 1415	1713 ± 1401	66.6	57.8	15.4	2.6	13.6	7.0	70 (38–114)	67 (39–110)
ProMISe Investigators [12]	2226 ± 1443	2022 ± 1271	53.3	46.6	18.1	3.8	8.8	3.8	NA[b]	NA[b]
Secondary objective										
Wang et al. [21]	4895 ± 210	2340 95	100	100	NA	NA	NA	NA	NA	NA
De Oliviera et al. [20].	NA[a]	NA[a]	49.0	56.9	29.4	7.8	45.1	15.7	NA	NA
EGDT Collaborative [22]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tian et al. [23]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yu et al. [24]	3300 ± 1210	3600 ± 1360	80.0	72.0	4.0	8.0	20.0	16.0	NA	NA
Lu et al. [25]	2809 ± 795	3608 ± 715	87.5	76.2	NA	NA	NA	NA	NA	NA

Data presented as mean ± SD or percentage (%) unless otherwise indicated. The primary objective included only those studies in which patients presented to the emergency department with septic shock ($n = 5$). The secondary objective included those studies in which the presenting source was the emergency department and the ward or ICU or where the source was not known ($n = 11$). The control for all analyses was usual care or another non-EGDT resuscitation strategy. For the ProCESS trial [8], data presented for the control group are usual care and protocol-based standard therapy groups combined

ProCESS Protocolized Care for Early Septic Shock, *ARISE* Australasian Resuscitation in Sepsis Evaluation, *ProMISe* Protocolised Management In Sepsis, *EGDT* early goal-directed therapy, *NA* not available, *IQR* interquartile range

[a] Median (interquartile range) for EGDT and control groups were 28 (20–40) and 5 (0–20) ml/kg, respectively

[b] All patients received antimicrobials prior to randomisation

modelling did not change any results (Supplementary Appendix Figs. S4–6). EGDT was associated with increased ICU admission (OR 2.19 [95 % CI 1.82–2.65]; $P < 0.001$) (Table 4; Fig. 3). However, there was no difference in ICU length of stay for those admitted (WMD −0.02 [95 % CI −0.47 to 0.43] days; $P = 0.93$) (Fig. 3). Hospital length of stay was also not different (WMD −0.28 [95 % CI −1.18 to 0.62] days; $P = 0.55$) (Table 4; Supplementary Appendix Fig. S7).

Patients with septic shock independent of presenting source

Mortality for the secondary objective was 23.4 % (572 of 2448 patients) in the EGDT group and 23.9 % (699 of 2930 patients) in the control group. EGDT did not reduce overall mortality (OR 0.94 [95 % CI 0.82–1.07]; $P = 0.33$). Heterogeneity was significant ($I^2 = 71$ %; $P < 0.001$). Post hoc analysis using a random-effects model did not change the results and there was no evidence of interaction between presenting source and EGDT in a random-effects meta-regression ($P = 0.51$) (Supplementary Appendix Fig. S8). There was no evidence of small study effects either by visual assessment of the funnel plot or by Egger's test ($P = 0.58$) (Supplementary Appendix Fig. S9).

Discussion

Our meta-analysis identified 11 randomised clinical trials evaluating EGDT versus usual care or an alternative non-EGDT resuscitation strategy among more than 5000 patients with septic shock. We found that, across the five studies of patients presenting to the ED with septic shock, EGDT was not associated with decreased mortality compared with usual care; however, EGDT was associated with increased admission to ICU.

In recent years, several meta-analyses evaluating EGDT reported a survival benefit in patients with septic shock [15–17]. Barochia et al. [17] found that bundled care incorporating EGDT was associated with an increase in survival [OR 1.91 (95 % CI 1.49–2.45)]. However, seven of the eight included studies were non-randomised before–after trials, of which four reported baseline imbalances between treatment groups. In many of these studies, compliance with the EGDT algorithm was also low yet an overall mortality benefit was observed,

Table 4 GRADE-style evidence profile for the effect of early goal-directed therapy in patients with septic shock presenting to the emergency department [26]

	No. of studies	No. of participants	Study limitations[c]	Quality assessment		Summary of findings				
				Heterogeneity I^2 (P value)	Precision[d]	Publication bias[e]	Relative effect (95 % CI)[f]	Assumed event rate[g]	EGDT event rate[h] (%)	Overall quality
Primary study mortality[a]										
Primary objective[b]	5	4735	Moderate	56.7 % (0.055)	NII	Unlikely	1.01 (0.88–1.16)	22.4 %	22.5	Moderate
Secondary objective	11	5378	Significant	70.7 % (<0.001)	NII	Unlikely	0.94 (0.82–1.07)	23.9 %	22.7	Low
28-day mortality	4	4330	Moderate	54.7 % (0.085)	NII	Possible	0.95 (0.82–1.10)	22.6 %	21.7	Moderate
90-day mortality	3	4063	Moderate	0 % (0.97)	NII	Possible	0.99 (0.80–1.15)	26.7 %	26.5	Moderate
In-hospital mortality	5	4744	Moderate	59.2 % (0.044)	NII	Unlikely	1.00 (0.87–1.16)	20.3 %	20.3	Moderate
Hospital length of stay	5	4740	Moderate	0 % (0.65)	NII	Unlikely	0.26 (−1.18 to 0.62)	11–17 days		Moderate
ICU admission	4	4480	Moderate	11.6 % (0.32)	NII	Possible	2.19 (1.82–2.65)	82.9 %	91.4	Moderate
ICU length of stay	4	3876	Moderate	0 % (0.58)	NII	Possible	−0.02 (−0.47 to 0.43)	5–6 days		Moderate
Receipt of MV	5	4715	Moderate	55.0 % (0.064)	NII	Unlikely	0.97 (0.86 to 1.10)	34.9 %	34.2	Moderate
Duration of MV	4	1625	Moderate	40.2 % (0.17)	NII	Possible	0.48 (−0.34 to 1.30)	5–9 days		Moderate
Receipt of vasopressors	5	4743	Moderate	78.9 % (0.001)	NII	Unlikely	1.25 (1.10–1.40)	60.5 %	65.6	Moderate
Duration of vasopressors	3	2984	Moderate	0 % (0.68)	NII	Possible	0.09 (−1.12 to 0.29)	2.4–2.5 days		Moderate
Receipt of RRT	3	4003	Moderate	0 % (0.52)	SI	Possible	0.99 (0.81–1.22)	10.1 %	10.1	Moderate
Duration of RRT	3	430	Moderate	0 % (0.95)	NII	Possible	−0.36 (−1.75 to 1.03)	5–9 days		Moderate

Analysis for the primary objective included only those studies in which patients presented to the emergency department with septic shock. Analysis for the secondary objective included those studies in which the presenting source was the emergency department and the ward or ICU or where the source was not known. The control for all analyses was usual care or another non-EGDT resuscitation strategy; for the ProCESS trial the control group was usual care and protocol-based standard therapy groups combined [8]. Secondary outcomes were evaluated for the primary objective only

ICU intensive care unit, *MV* mechanical ventilation, *RRT* renal replacement therapy, *NII* no important imprecision, *SI* some imprecision, *CI* confidence intervals, *EGDT* early goal-directed therapy

[a] If mortality at more than one time was reported, we used the primary mortality outcome of each included study

[b] Effect estimate determined using usual care and protocol-based standard therapy groups combined for the ProCESS trial [8]. The effect estimate was not different using the usual care group only and excluding the Jones trial (control group lactate clearance) [19] (OR 0.97 [95 % CI 0.84–1.12])

[c] Study limitations were determined using the results of the independent risk of bias assessment (Table 4). All studies were adjudged as having at least moderate limitations due to the lack of blinding

[d] Some imprecision determined to be present when the 95 % CI did not exclude a 20 % relative difference in the effect estimate

[e] Formal assessment of publication bias was unable to be performed (other than for the secondary objective) due to the small number of included studies. However, given the extensive search strategy, was adjudged to be unlikely, other than for outcomes of interest for which there was incomplete reporting and selective reporting was considered to be possible

[f] Effect estimates for mortality and receipt of organ support are reported as odds ratio and for length of stay and duration of organ support weighted mean difference (days)

[g] Assumed event rates for mortality and receipt of organ support are the event rates from the control groups of all included studies and for length of stay and duration of organ support the ranges of the mean values from the control groups across the included studies

[h] EGDT event rates for mortality and receipt of organ support are calculated by applying the estimated odds ratios to the assumed event rates

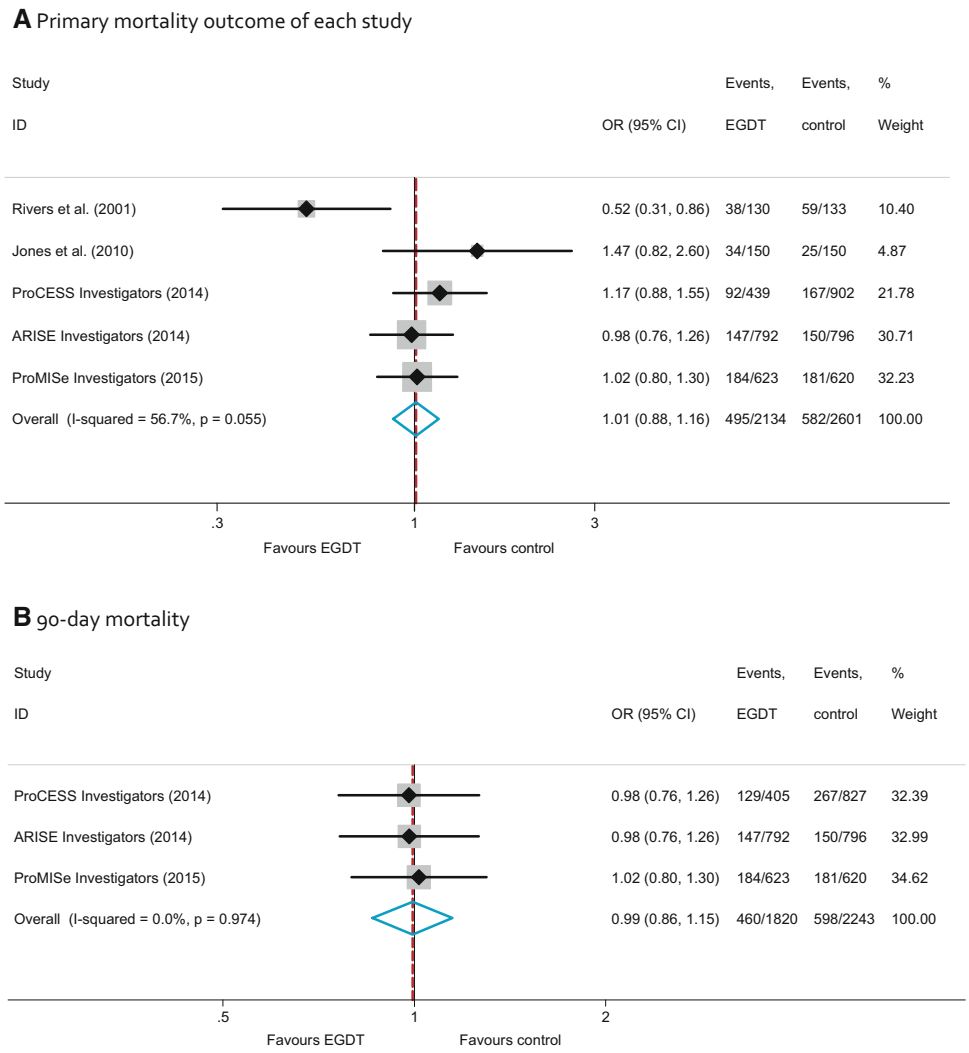

Fig. 2 Effect of EGDT on mortality in patients presenting to the emergency department with septic shock. **a** Primary mortality outcome of each study. **b** 90-day mortality. *EGDT* early goal-directed therapy, *OR* odds ratio, *CI* confidence interval. The control was usual care or another non-EGDT resuscitation strategy. Fixed-effect model: the *individual points* denote the OR of each study and the *lines* either side the 95 % confidence intervals. The *vertical lines* denote the null effect. The control for the ProCESS trial [8] includes both usual care and protocol-based standard therapy groups combined. Analysis comparing EGDT with the ProCESS usual care group only and excluding the Jones trial (control group lactate clearance) [19] did not change the result (OR 0.97 [95 % CI 0.84–1.12; I^2 56.5, $P = 0.08$]

suggesting that factors other than the specific resuscitation protocol influenced outcomes. Similarly, Wira et al. [16] reported improved survival across 15 studies; although, again, the risk of bias was high with only one randomised trial included.

Finally, Gu et al. [15] found a decrease in mortality with the early institution of goal-directed therapy [relative risk 0.83 (95 % CI 0.71–0.96)] across seven studies, of which two evaluated a resuscitation strategy that did not incorporate $ScvO_2$ monitoring (including one study of supra-normal haemodynamic optimisation conducted over 20 years ago), one included a different target population (patients with multiple organ dysfunction) and another was not a randomised trial. When the two studies of EGDT conducted in patients presenting to the ED with septic shock were analysed [1, 8] mortality was not decreased [relative risk 0.86 (95 % CI 0.52–1.44)]. The results of our meta-analysis, which focuses exclusively on randomised clinical trials and which includes two additional, pivotal, multicentre randomised clinical trials [10, 12], confirm the lack of a survival benefit associated with the implementation of EGDT in patients presenting to the ED with septic shock compared to either usual care or an alternative resuscitation strategy. However, EGDT was associated with an increased intensive care admission rate. This increased utilisation of healthcare resources was consistent across a variety of hospital settings (tertiary referral, metropolitan, rural) and geographical regions, despite substantial variation in hospital and intensive care resources [27]

Strengths and limitations

We included the recent ProCESS [8], ARISE [10] and ProMISe [12] harmonised, multicentre randomised clinical trials to better assess the evidence of EGDT in patients with septic shock. In addition to including these

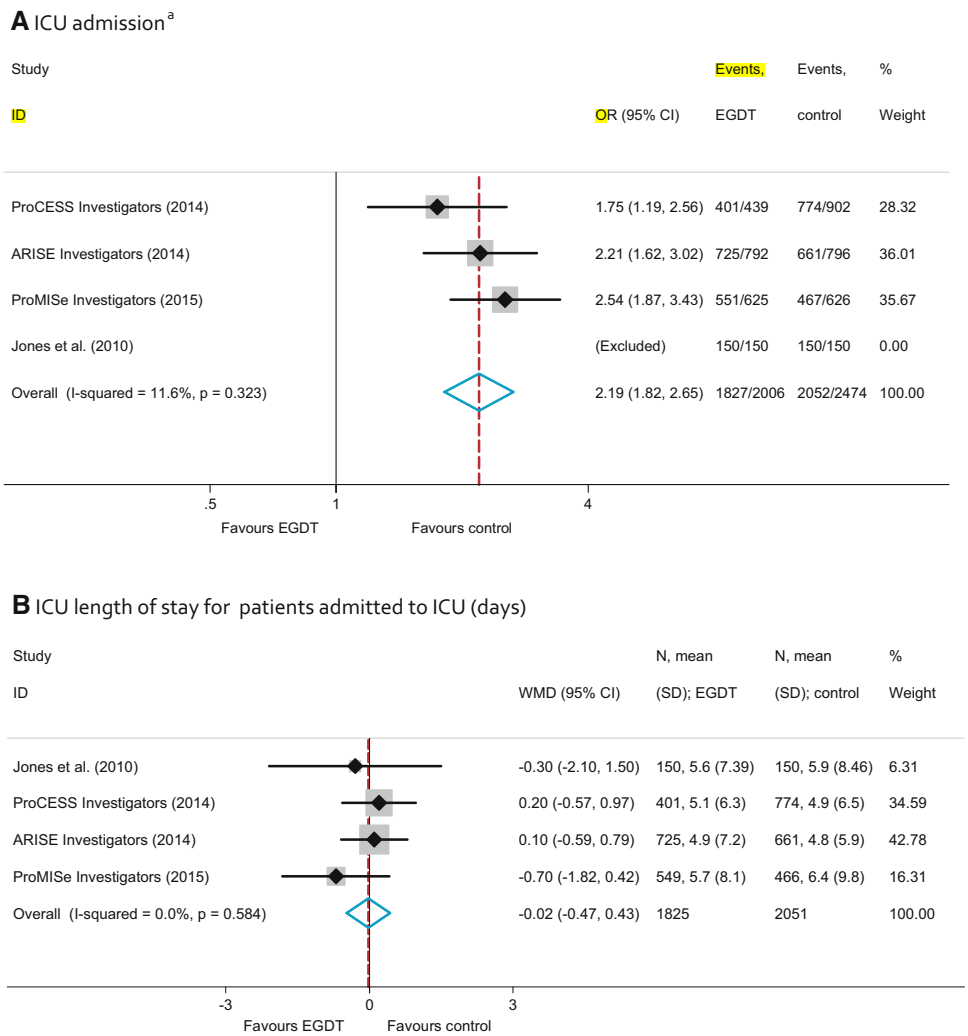

Fig. 3 Effect of EGDT on ICU utilisation in patients presenting to the emergency department with septic shock. **a** ICU admission[a]. **b** ICU length of stay for patients admitted to ICU (days). *ICU* intensive care unit, *EGDT* early goal-directed therapy, *OR* odds ratio, *CI* confidence interval, *WMD* weighted mean difference, *SD* standard deviation. The control was usual care or another non-EGDT resuscitation strategy. Fixed-effect model: the *individual points* denote the OR or WMD of each study and the *lines* either side the 95 % confidence intervals. The control for the ProCESS trial [8] includes both usual care and protocol-based standard therapy groups combined. [a]"Favours EGDT" denotes lower ICU admission rate for the EGDT group and "Favours control" denotes higher ICU admission rate for the EGDT group

three studies, our search strategy was broad and included all studies of EGDT irrespective of language; however, we could not confirm several key design features with some non-English manuscripts. Although investigators of the three most recent trials of EGDT are authors of our report, we used a structured and accepted assessment approach, the Cochrane Collaboration tool, with independent assessors of the risk of bias. This approach, coupled with excluding observational studies, reduced the risk of bias in our estimate of the treatment effect.

Our study has several limitations. Reporting of mortality outcomes across the included studies was not uniform. Ninety-day mortality was the primary study outcome in only two studies (and reported as a secondary outcome in an additional one study) and only two of the 11 studies were assessed as having a low risk of bias (other than for blinding of participants and personnel). The effect of individual patient confounders, as well as international and local variation in healthcare services (e.g. number of ED presentations and threshold for hospital and ICU admission), how EGDT was delivered across the sites and the nature of usual care can also not be established in our trial-level meta-analysis. However, we plan an individual patient data meta-analysis of the three large harmonised trials to allow more detailed and specific questions including the overall effect of EGDT compared with other forms of resuscitation, the role of individual elements of the EGDT algorithm and the effect of EGDT across countries and hospital settings. We will also explore the potentially differential effect of EGDT across clinically important subgroups (Protocolised Resuscitation In Sepsis individual patient data Meta-analysis [PRISM]; ClinicalTrials.gov.NCT02030158).

Conclusions

Our meta-analysis of all published randomised clinical trials of EGDT does not show improved survival for

patients randomised to receive EGDT compared to usual care or to less invasive alternative haemodynamic resuscitation protocols. EGDT is, however, associated with increased admission to ICU. Our findings do not support the systematic use of EGDT in the management of all patients with septic shock or its inclusion in the Surviving Sepsis Campaign guidelines.

Conflicts of interest The authors declare no conflict of interest.

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