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Review Article

Effects of goal directed therapy for adult patients in sepsis: a systemic review and meta-analysis of randomized controlled trials

Xiabing Lang, Yi Yang, Ping Zhang, Wenhua Lei, Jianghua Chen

Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, P. R. China

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Abstract: Backgroud: The effectiveness of goal directed therapy (GDT) as a key strategy to decrease mortality is uncertain among patients with sepsis or septic shock. Objective and methods: We conducted a systematic review and meta-analysis using the MEDLINE database (1996 through April 2015), EMBASE (1988 through April 2015). Randomized controlled trials comparing outcome with or without GDT to decrease mortality among adult patients with sepsis or septic shock were identified. Results: 15 studies (5356 participants) were included. GDT decreased the overall mortality for adult patients with sepsis compared to the control group (risk ratio [RR]=0.86; 95% CI=0.76 to 0.97; P=0.02; I^2=56%) with marginal statistical significance. GDT also associated with shorter length of ICU stay (mean difference, -1.56; 95% CI=-3.06- -0.07; P<0.00001), more dobutamine use (RR=2.80; 95% CI=1.24-6.33; P=0.01; I^2=95%). But there was no difference in length of hospital stay, incidence of MODS, renal dysfunction and amount of intravenous fluid. The timing and pretreatment prior to randomization for resuscitation suggested that a mortality benefit was enhanced in the subgroup of EGDT without administration of fluids prior to randomization (6 trials; RR=0.73; 95% CI=0.65-0.82; P<0.00001; I^2=0%). No benefit of GDT was seen if there was a pretreatment with intravenous fluids prior to randomization (3 trials; RR=1.02; 95% CI=0.91-1.15; P=0.72; I^2=0%) or GDT more than 6 hours (6 trials; RR=0.90; 95% CI=0.66-1.23; P=0.53; I^2=59%). Conclusion: GDT might be beneficial for the adult patients undergoing sepsis. Early fluid resuscitation rather than the specific protocols for resuscitation have more benefit in sepsis management.

Keywords: Goal directed therapy, sepsis, septic shock, mortality, intravenous fluid, organ failure, meta

Introduction

Sepsis and septic shock are the most common and severe cause of morbidity and mortality among critically ill patient [1]. The reported annual incidence in adults is up to 300 cases per 100,000 population [2-4]. It often complicates with multiple organ dysfunction syndrome (MODS), especially acute kidney injury (AKI), leading to a worse prognosis.

Goal-directed therapy (GDT) is therapeutic measures including intravenous fluids, red cell transfusion and vasoactive drug administration, aiming to achieve specific haemodynamic goals. GDT has been confers a protective action on surgical patients to decreased perioperative complications [5], including the risk of renal dysfunction [6]. It has also been used for sepsis or septic shock in the intensive care unit (ICU) or emergency department (ED). The Surviving Sepsis Campaign guidelines recommend early initiation of GDT (EGDT), which the GDT is initiated within 6 hours for septic patient [7]. This is largely supported by the results of the Rivers and colleagues [8]. This single-center randomized controlled trial (RCT) showed the significantly reduction of mortality in those treated according to a 6-hour protocol of EGDT compared to the usual care group (30.5% vs. 46.5%). However, 3 large RCTs lately had conflicting results [9-11]. Published data are still limited and drawing conclusions from them remains controversial. Moreover, the protecting effect of GDT beyond the initial resuscitative period to decrease MODS is still elusive.

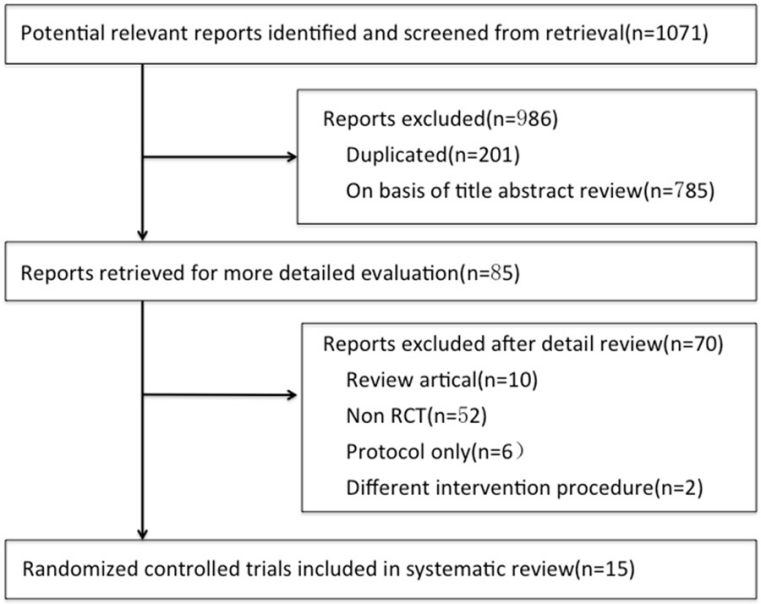

Figure 1. Flowchart of article selection. Abbreviation: RCT, randomized controlled trial.

To addressing these questions, we systematically evaluating the available evidence and performed a meta-analysis of RCTs. We focused on the effects of GDT (or EGDT) on the survival of adult patients with sepsis or septic shock. As the secondary objectives, we also assessed the differences in the length of ICU and hospital stays, the incidence of organ dysfunction, the intravenous fluid and dobutamine use in these trials.

Materials and methods

Search strategy

Electronic searches were performed using MEDLINE (1966 through April 2015) and EMBASE (1988 through April 2015). The following Medical Subject Headings terms and text words were used: sepsis, septic*, pyemia*, pyohemia*, pyaemia*, goal-directedtherapy, goal-directed resuscitation, GDT, fluid administration. We also searched the references of the included studies and recent review articles. There were no language restrictions. To ascertain the inclusion criteria conformity, 2 of the authors (P.Z. and L.WH.) independently analyzed titles and abstracts of these articles. The full text was reviewed if the title and abstract was unclear with regard to its admissibility.

We used the Cochrane Collaboration methodology to undertake [12], and follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to report our meta-analysis [13]. Since it was a meta-analysis, there was no need to have ethical approval and patient consent.

Study selection

Eligible studies had the following characteristics: (1) they were randomized controlled trials of GDT for sepsis or septic shock; (2) GDT was defined as therapeutic measures including intravenous fluids, red cell transfusion and vasoactive drug administration to achieve specific haemodynamic goals. The GDT must have an explicit protocol; (3) Trial participants should be adult patients with sepsis or septic shock or a subgroup of the trial population; (4) The studies had to reported the overall mortality rate.

The primary outcome measure was the overall mortality, which means the hospital mortality or the only data of mortality if there was only one time point. Secondary outcome measures included the length of ICU and hospital stay, incidence of organ dysfunction, the amount of intravenous fluid and incidence of dobutamine use.

Data extraction

We used a standardized data extraction form and two reviewers (P.Z. and L.XB.) extracted data separately from the including studies. When there were any discrepancies between the 2 reviewers, an arbitrator (Y.Y.) made a decision by discussion with them. And they also assessed each studies and extracted data about demographic characteristics of patients, clinical setting, protocol for GDT and control therapy, hospital mortality, incidence of organ dysfunction, the amount of intravenous fluids and incidence of dobutamine use.

Study validity assessment

Studies included in the meta-analysis were evaluated for methodological quality using the

Table 1. Demographic data of included trials

Author	Year	Type of patients	Clinical setting	No. of patients in GDT group	No. of patients in control group	Goal in GDT group	Goal in control group	Mortality endpoint
Alia	1999	Severe sepsis or septic shock	ICU	31	32	DO_2I>600 ml/min/m^2, MAP>60 mmHg	DO_2I>330 ml/min/m^2, MAP>60 mmHg	ICU
ARISE	2014	Septic shock	ED & ICU	792	796	CVP≥8 to 12 mmHg, MAP≥65 to 90 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%, Haematocrit≥30%	Study materials will not be provided and $ScvO_2$ measurement will not be performed.	90 d
Chen	2007	Severe sepsis	ICU	58	65	CVP≥8 to 12 mmHg, MAP≥65 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	CVP≥8 to 12 mmHg, MAP≥65 mmHg, UO≥0.5 ml/kg/h	ICU
Gattinoni L	1995	Sepsis	ICU	124	57	CI≥4.5 L/min/m^2, SvO_2>70%, MAP≥60 mmHg, CVP 8 to 12 mmHg, UO≥0.5 ml/kg/h	CI≥4.5 L/min/m^2, MAP≥65 mmHg CVP 8 to 12 mmHg UO≥0.5 ml/kg/h	ICU
Hayes MA	1994	Septic shock	ICU	24	23	CI≥4.5 L/min/m^2, DO_2 600 ml/min/m^2, VO_2>170 ml/min/m^2	Standard care	Hospital
He	2007	Septic shock	ICU	98	105	CVP≥8 to 12 mmHg, MAP≥65 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	Standard care	Hospital
Lin	2006	Septic shock	ICU	108	116	CVP≥8 to 12 mmHg, MAP≥65 mmHg, UO≥0.5 ml/kg/hr	Guidelines for hemodynamic support without any fixed algorithm	Hospital
ProCESS	2014	Septic shock	ED	439	456	CVP≥8 to 12 mmHg, MAP≥65 to 90 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	Standard care	Hospital
ProMISe	2015	Sepsis	ED	623	620	SpO_2≥93%, CVP≥8 to 12 mmHg, MAP≥65 to 90 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%, Haematocrit≥30%	Usual care	90 d
Rivers	2001	Severe sepsis or septic shock	ED	130	133	CVP≥8 to 12 mmHg, MAP≥65 to 90 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	CVP≥8 to 12 mmHg, MAP≥65 mmHg, Uo≥0.5 ml/kg/h	Hospital
Tuchschmidt J	1992	Septic shock	ICU	26	25	CI≥6 L/min/m^2, SAP≥90 mmHg	CI≥3 L/min/m^2, SBP≥90 mmHg	14 d
Wang	2006	Septic shock	ICU	16	17	CVP≥8 to 12 mmHg, MAP≥65 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	MAP≥65 to 90 mmHg, UO≥0.5 ml/kg/h	14 d
Yan	2010	Severe sepsis or septic shock	ICU	157	146	CVP≥8 to 12 mmHg, MAP≥65 mmHg, SBP≥90 mmHg, UO≥0.5 ml/kg/h, $ScvO_2$≥70%	CVP 8 to 12 mm Hg, SBP> 90 mmHg, MAP≥65 mm Hg, UO≥0.5 ml/kg/h	ICU
Yu M	1993	Sepsis	ICU	30	22	DO_2I>600 ml/min/m^2, SBP>100 mmHg	DO_2I 450 to 550 ml/min/m^2, SBP>100 mmHg	30 d
Yu M	1998	Sepsis	ICU	58	29	SBP≥100 mmHg, UO>50 mL/h, SvO_2 of >65%, DO_2I>600 ml/min/m^2 MAP>60 mmHg	SBP≥100 mm Hg, UO>50 mL/h, SvO_2 of >65%, DO_2I 450 to 550 ml/min/m^2	ICU

Abbreviations: ProCESS, Protocolized Care for Early Septic Shock; ARISE, Australasian Resuscitation In Sepsis Evaluation Randomised Controlled Trial; ProMISe, Protocolised Management in Sepsis; ED, Emergency department; ICU, Intensive care unit; GDT, Goal-directed therapy; CI, Cardiac index; CVP, Central venous pressure; DO_2, Oxygen delivery; DO_2I, Oxygen delivery index; MAP, Mean arterial pressure; SBP, Systolic blood pressure; $ScvO_2$, Central venous oxygen saturation; SvO_2, Mixed venous oxygen saturation; UO, Urine output; VO_2, Oxygen consumption.

Table 2. Quality assessment of included trials

Study	Year of publication	Randomization method	Allocation concealment	Blinding	Withdrawals and dropouts described	Intention-to-treat analysis
Alia	1999	A table of random numbers.	Sealed envelopes	Single blind	Yes	Yes
ARISE	2014	Permuted-block method	Centralized telephone interactive voice-response system	Single blind	Yes	Yes
Chen	2007	Unclear	Unclear	Single blind	Yes	Yes
Gattinoni	1995	Permuted-block algorithm	Telephone	Single blind	Yes	Yes
Hayes	1994	A table of random numbers.	Unclear	Single blind	Yes	Yes
He	2007	Unclear	Unclear	Single blind	Yes	Yes
Lin	2006	Computer-generated blocks	Sealed envelopes	Single blind	Yes	Yes
ProCESS	2014	Variable block sizes of 3, 6, or 9	Centralized Web-based program	Single blind	Yes	Yes
ProMISe	2015	Randomized permuted blocks	24-hour telephone ran- domization	Single blind	Yes	Yes
Rivers	2001	Computer-generated blocks	Sealed envelopes	Single blind	Yes	Yes
Tuchschmidt	1992	Unclear	Unclear	Single blind	Yes	Yes
Wang	2006	Unclear	Unclear	Single blind	Yes	Yes
Yan	2010	Random numbers by SAS program	Unclear	Single blind	Yes	Yes
Yu M	1993	A table of random numbers.	Unclear	Single blind	Yes	Yes
Yu M	1998	Unclear	Unclear	Single blind	Yes	Yes

Abbreviations: ProCESS, Protocolized Care for Early Septic Shock; ARISE, Australasian Resuscitation In Sepsis Evaluation Randomised Controlled Trial; ProMISe, Protocolised Manag.

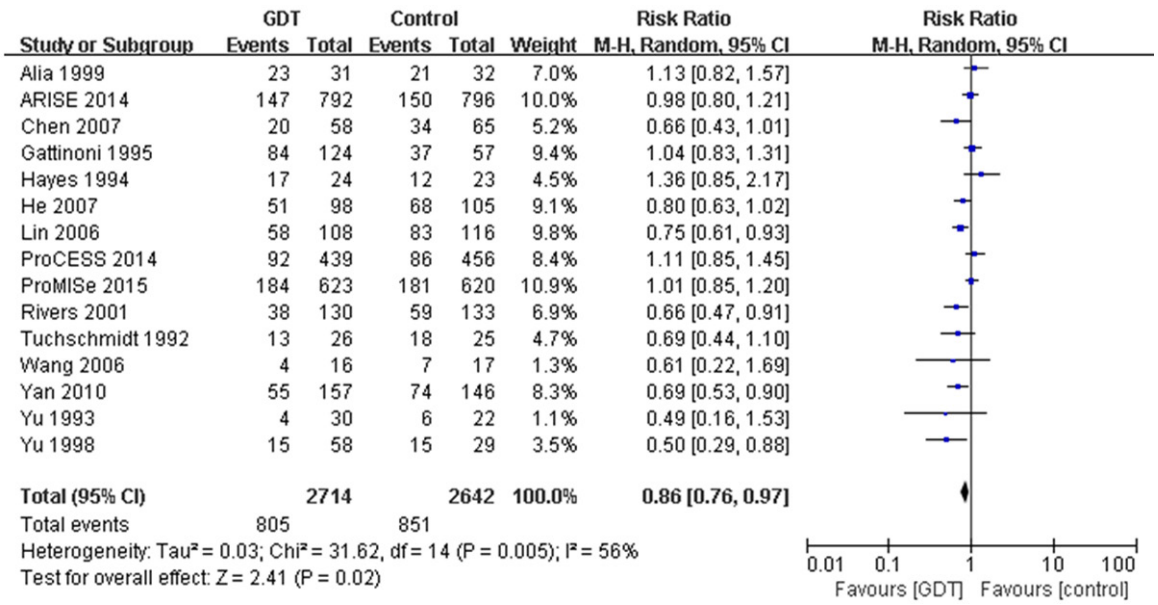

Figure 2. Comparison of GDT versus control group for the overall mortality. Abbreviations: GDT, goal directed therapy; CI, confidence interval; M-H, Mantel-Haenszel method.

criteria of the Jadad composite scale (randomization, blinding and withdrawals, and drop outs) [14]. Allocation concealment and intention-to-treat analysis also were assessed.

Data analysis and synthesis

We used risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and mean difference with 95% CI for continuous outcomes. To determine the robustness of our pooled effects, we compared our primary analysis in random-effects model by the Mantel-Haenszel method. The mean difference was analysis with Intervese variance method. We assessed statistical heterogeneity using I^2 tests and determined the percentage of total variation across studies using Higgins I^2 statistic. I^2 values >25%, 50%, and 75% were considered evidence of low, moderate, and severe statistical heterogeneity, respectively. Analyses were carried out with the RevMan 5.3 software.

Results

Search results and study characteristics

The search strategy identified 1071 articles, of which 986 were excluded because they were either nonrandomized studies or evaluated interventions or outcomes that were not relevant to this review. Full-text assessment of 85 potentially relevant articles identified 15 eligible trials (**Figure 1**) [8-11, 15-25]; all 15 were full-length articles.

There were 4115 participants in total enrolled in the 15 studies, including 3 studies in patients enrolled from the ED [8, 9, 11], 11 studies in patients enrolled from ICU [15-25], and 1 studies in patients enrolled from both emergency department and ICU [10]. The published date was from 1992 to 2015. The GDT method varied among studies: EGDT for resuscitation was reported in 9 trials [8-11, 21-25], while late or unclear timing of GDT was assessed in 6 trials [15-20]. Among the EGDT group, 3 trails [9-11] conducted a pretreatment with intravenous fluids prior to randomization. All trails reported the overall mortality while only 7 trails mentioned MODS [8, 16, 17, 20-24] and 6 trails mentioned the renal dysfunction [9, 16, 18-21]. Key characteristics of the included studies are summarized in **Table 1**.

Quality assessment and risk of bias in included studies

The quality of the included studies was assessed separately by 2 of the authors (Y.Y. and C.JH) using criteria of the Jadad composite scale. 8 (53%) studies met allocation concealment criteria [8-11, 18, 20, 21], and all (100%) studies met the intention-to-treat analysis crite-

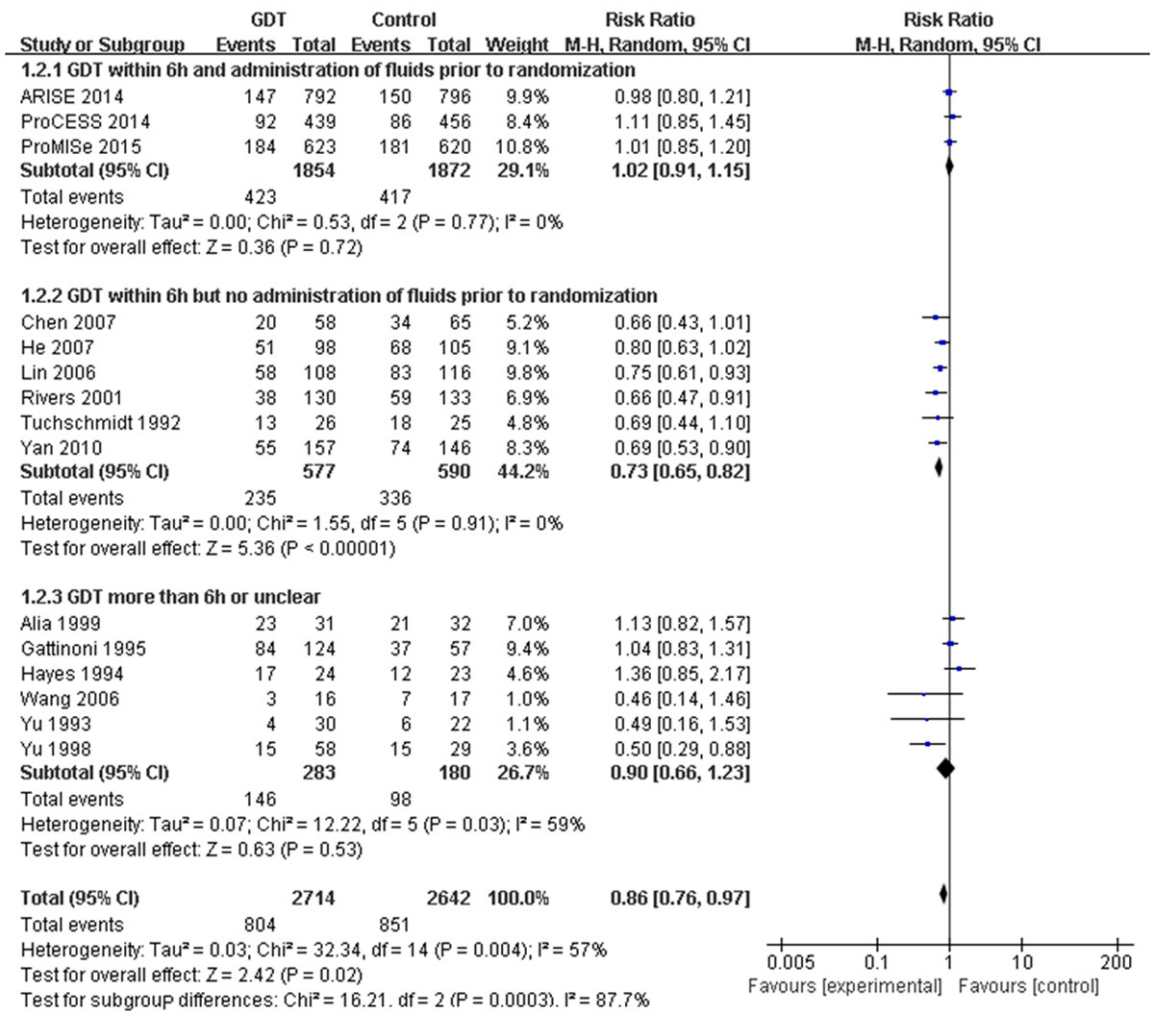

Figure 3. Subgroup analyses of overall mortality. Abbreviations: GDT, goal directed therapy; CI, confidence interval; M-H, Mantel-Haenszel method.

ria. The overall details of quality assessment are listed in **Table 2**.

Primary outcome: overall mortality

The data of overall mortality were available in all 15 trails. In the GDT group, the overall mortality was 29.7%, while in the control group the mortality was significantly higher, which was 32.2% (RR=0.86; 95% CI=0.76-0.97; P=0.02; I^2=56%) (**Figure 2**). Then we conducted the sensitivity analysis by omit study one by one, and found exclusion of any study did not change the RR much. And there was no evidence of publication bias by assessing funnel plot (**Figure 4**).

Subgroup analysis

It is important to note that the present result should be regarded with caution because different initiated time and resuscitation protocol were applied. So we analyzed the subgroup according to the timing of GDT and the pretreatment prior to randomization for resuscitation, which suggested that a mortality benefit was seen only in the subgroup of EGDT but no administration of fluid prior to randomization (6 trials; RR=0.73; 95% CI=0.65-0.82; P<0.00001; I^2=0%) (**Figure 3**). No difference was seen in the subgroup of late or unclear timing of GDT (7 trials; RR=0.90; 95% CI=0.66-1.23; P=0.53; I^2=59%), or in the subgroup of EGDT and administration of fluids prior to randomization (3 trials; RR=1.02; 95% CI=0.91-1.15; P=0.72; I^2=0%).

Length of ICU and hospital stays

Six trials (n=2757 participants) reported mean length of ICU stays and 5 trials (n=2484) report-

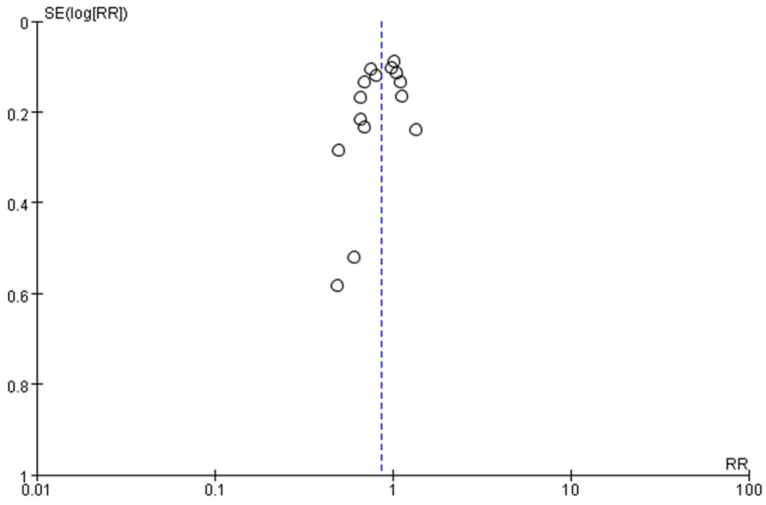

Figure 4. Funnel plot of the effect goal-directed therapy on overall mortality.

ed mean hospital stays. The length of ICU stay of GDT group was shorter than the control group (mean difference, -1.56; 95% CI, -3.06, -0.07; P=0.04). However, there was no significant difference between the 2 arms in length of hospital stay (mean difference, -0.36; 95% CI, -0.66, 1.38; P=0.49). (Supplementary Figures 1, 2).

Incidence of MODS

Data regarding MODS were available for 7 trials included in the meta-analysis. Of patients undergoing GDT, the risk of MODS was no difference compared to the control group (RR=0.78; 95% CI=0.60-1.01; P=0.06). There was statistical heterogeneity noted among the included trials (heterogeneity X^2=19.44; I^2=69%; P=0.003; Supplementary Figure 3).

Incidence of renal dysfunction

Data regarding renal dysfunction incidence were available for 6 trials included in the meta-analysis. Of patients undergoing GDT, the risk of dysfunction was no difference compared to the control group (RR=0.94; 95% CI=0.73-1.20, P=0.60). There was low statistical heterogeneity noted among the included trials (heterogeneity X^2=7.01; I^2=29%; P=0.22; Supplementary Figure 4).

Use of dobutamine

There are 8 trials reported data on dobutamine use. There was high s heterogeneity among those trials, even though GDT was significantly associated with dobutamine use (RR=2.80; 95% CI=1.24-6.33; P=0.01; I^2=95%; Supplementary Figure 5).

Mean intravenous fluid volume

There are 5 trails reported available data on mean intravenous fluid volume within the first 6 hours. In those trails GDT was no significantly associated with intravenous fluid volume within the first 6 hours (mean difference 999.08; 95% CI=-181.43-2179.58; P=0.10; I^2=100%; Supplementary Figure 6).

Discussion

GDT is sure to have benefit in high-risk surgical patients [5, 6], and we wonder to know its benefit in critically ill patients with sepsis. In this present study, we reviewed existing randomized controlled trials to test the hypothesis that GDT gain the mortality benefits. We included 15 RCTs, in which 3 were the latest and largest trails. The result showed GDT can reduce overall mortality significantly, although the heterogeneity was high. So the in-depth subgroup analysis conducted and showed that benefit was only in the subgroup of EGDT but no administration of fluid prior to randomization. Besides, GDT could reduce the length of ICU duration.

GDT has been proposed because clinicians should consider of both the benefit and the harmful effects of resuscitation. It includes intravenous fluids, red cell transfusion and vasoactive drug administration to achieve specific haemodynamic goals. GDT is proved to have important benefit in surgical patients. However, its benefit in sepsis patients was not as much definite. Several trials and meta-anlysis support the guidelines of ACCM/PALS with $ScvO_2$ goal-directed resuscitation [26-28]. However, the results of the latest three trails (ProCESS, ARISE and ProMISe) [9-11] had different sound. This provoked concerns about comparing them with the other trails included in previous meta analysis [27]. The high risk of bias due to the uncertain methodology of some of the trials cannot be eliminated. Even with the subgroup analysis of GDT within 6 hours, there

was still low statistical heterogeneity. Therefore, along with the new randomized controlled trials published, an updated meta-analysis evaluating the effect of GDT for the treatment of sepsis was needed.

There is no doubt the timing of GDT should be considerate when performed the subgroup analysis. And considering of the fluids given prior to randomization in the latest three trials, the 'usual care' appears to have early fluid resuscitation. Therefore, we used both the timing of GDT and the pretreatment prior to randomization for resuscitation to perform the subgroup analysis. The result showed that benefit was only in the subgroup of EGDT but no administration of fluid prior to randomization. When the control group had early fluid resuscitation, the mortality benefit of GDT disappeared. And by conducted the subgroup analysis, we reduced the heterogeneity a lot. Certainly, this reflected the impact of early fluid resuscitation rather than the specific protocols for resuscitation in sepsis management.

We and others suggest that GDT significantly reduces overall mortality in patients with sepsis. However, the secondary outcomes like the length of ICU and hospital stays, renal dysfunction, MODS should also be considerate. Here we try to figure it out in our analysis. We found the GDT group had shorter length of ICU duration. However, the available raw data from these trials were insufficient to draw a certain conclusion because of the high heterogeneity. Likewise, we did not find a significant reduction in MODS and renal dysfunction in the GDT group compared with the control group.

Although our meta-analysis provided information more about the details of GDT in septic patients, the present meta-analysis had several limitations that should be considered. First, as described earlier, the protocols adopted in the trials included in the present meta-analysis were different. Although all the adopted protocols of GDT focus on the fluid management are similar, and we have accounted for this heterogeneity by using a random-effects model and performing subgroup analysis, we still should use caution when drawing conclusions. Besides, we didn't consider the effect of other therapy such as initiation of antibiotics on mortality. Secondary, outcomes of the included trials were different. Most trails use the in-hospital mortality but still some trails has different endpoint. Moreover, although many trials reported length of ICU and hospital stay, MODS and kidney dysfunction events, and the fluid and dobutamine use in the case and control groups, there might still be outcome reporting bias.

GDT might be beneficial for the adult patients undergoing sepsis. Early fluid resuscitation rather than the specific protocols for resuscitation have more benefit in sepsis management.

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Disclosure of conflict of interest

None.

Address correspondence to: Jianghua Chen, Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, P. R. China. Tel: +8657 187 236 992; Fax: +8657 187 236 992; E-mail: chenjianghua@zju.edu.cn

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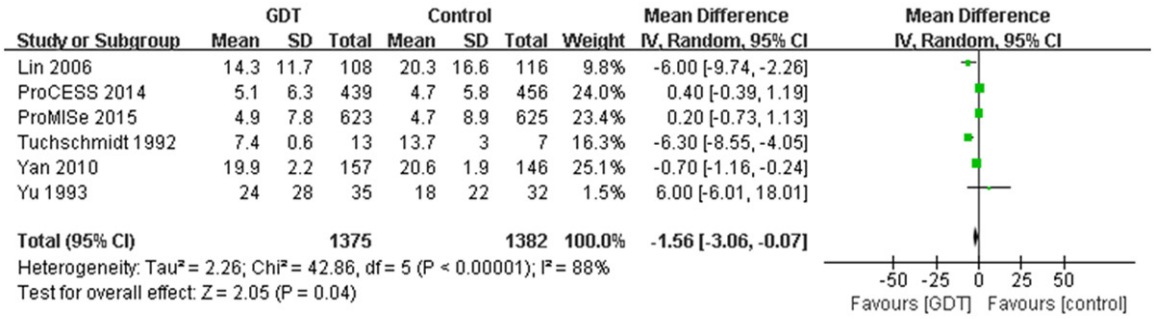
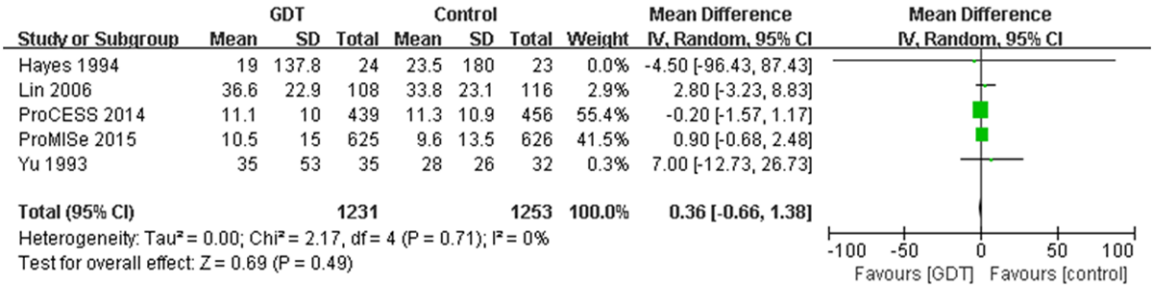
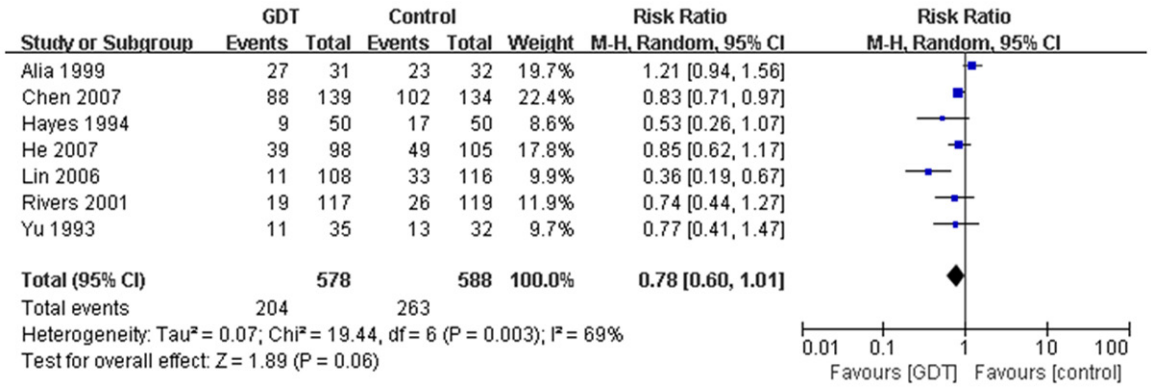


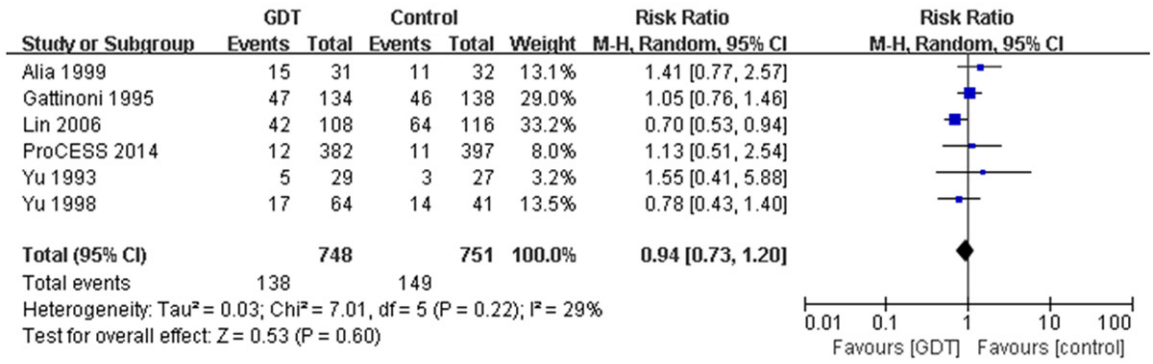
Supplementary Figure 1. Meta-analysis of mean difference for length of ICU stay.



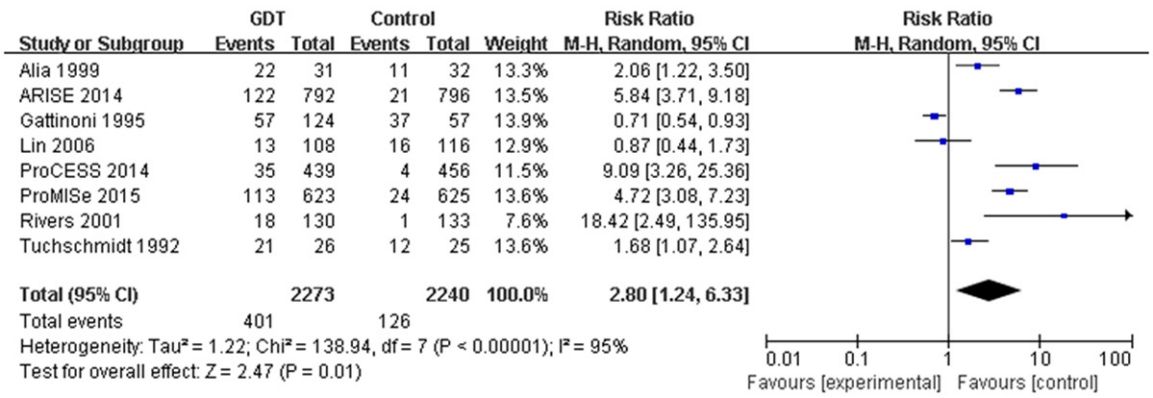
Supplementary Figure 2. Meta-analysis of mean difference for length of hospital stay.



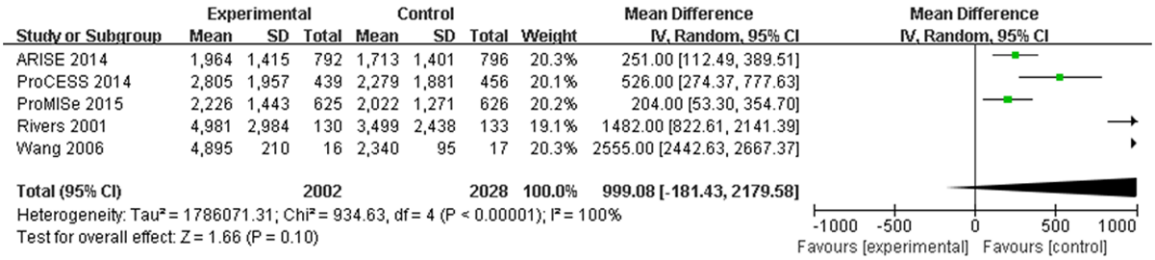
Supplementary Figure 3. Meta-analysis of incidence of MODS.



Supplementary Figure 4. Meta-analysis of incidence of renal dysfunction.



Supplementary Figure 5. Meta-analysis of incidence of dobutamine use.



Supplementary Figure 6. Meta-analysis of mean difference for intravenous fluid volume.