ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>The effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomized controlled trials</th>
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<tr>
<td>AUTHORS</td>
<td>Yu, Hong; Chi, Dongmei; Wang, Siyang; Liu, Bin</td>
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VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Emanuel Rivers</th>
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<td>Henry Ford Hospital</td>
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<td>I currently perform research in the same area of expertise.</td>
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<td>REVIEW RETURNED</td>
<td>12-May-2015</td>
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GENERAL COMMENTS

The ProCESS, ARISE and ProMISE trials were not complete replications of EGDT and they acknowledged these findings. These studies essentially addressed the need for CVP monitoring in early resuscitation.

When adjusted for illness severity, all trials after EGDT reveal:

a. A significant decrease in mortality, equivalency, and no harm compared to EGDT.

b. An unexpected low mortality rate which renders them underpowered.

c. According to all historical data reported in each trial, mortality has decreased 10-20% in all studies showing that early intervention (EGDT) is effective.

Methodology Concerns

These trials were conducted 8 years after the EGDT trial lasting 4 to 8 years in duration.

a. The SSC guidelines were published in 2004, 2008, and 2012 during the trial conduction.

b. Lactate screening and antibiotics were standard care prior to enrollment and required, not in the EGDT study.

c. Sudden cardiopulmonary events were eliminated as a cause of mortality and not acknowledged after the EGDT study.

d. Pre-hospital care, sepsis alerts, rapid response systems, telemedicine, and palliative care have evolved since EGDT and have changed mortality.

e. 4-6 hour rules to decrease ED overcrowding in ARISE and ProMISE trials and ICU admission in less in less than hours. The EGDT patients stayed in the ED for a minimum of 6-8 hours.

Enrollment considerations compared with the EGDT trial:
a. The fluid challenge was 1 liter not 20-30 cc/kg, 2 fold greater use of vasopressors.  
b. APACHE II scores were lower.  
c. High rates of exclusion of over 50% eligible patients.  
d. Convenience enrollment during time of optimal resources.  

Usual or control group care must be addressed:  
a. CVC and complete compliance rates were over 50% in all treatment groups including usual care.  
b. Pre-existing sepsis protocols in ProCESS, the Sepsis Six and ICU initiatives in ANZICS  
c. Steroid use was present in 8-37% of patients, even before randomization.  
d. Delays in RB compliance still improves outcomes after ICU admission.  
e. Lack of blinding in all groups and studies compared to original EGDT study. This is erroneous reported in this manuscript. This is an important source of bias.  
f. Rapid admission to the ICU in all trials and not an ED-based study compared to 6-8 hours in the EGDT study.  

Illness severity greater in the EGDT study:  
a. Greater co-morbidities and increased age.  
b. Two-fold greater use of mechanical ventilation.  
c. Shock severity-Lower ScvO2 increased lactate  

Prospective observational studies and meta-analysis (over over the last decade) number over 20,000 patients:  
a. Similar baseline mortality and mortality reduction to the original EGDT.  
b. Are the results of the last 3 trials representative of reality?  
c. Observational trials of this size are equivalent to RCT’s.  

No Kappa (inter-rater agreement) coefficient to support their screening and inclusion process  

There is no published protocol in the usual care groups. As PRISMA statement refers Without a protocol that is publicly accessible, it is difficult to judge between appropriate and inappropriate modifications on statistical analysis and eligibility criteria.  

Assess the confidence on their estimate using the GRADE approach of their estimates is showing  
a. adequate quality of evidence  
b. High heterogeneity,  
c. High indirectness (high differences between control groups mortality between Rivers and harmonized trials)  
d. high Impression (based on their 95% confidence interval estimates EGDT could provide a 40% reduction in mortality or increase mortality by 7%), even when the largest portion of the meta analysis favor EGDT they comment that there are differences in mortality  
e. Unable to evaluate publication bias but they failed to provide gray literature and search for unpublished data.  

**REVIEWER**  
John C. O'Horo  
Mayo Clinic  
Rochester, MN  
United States
Yu et al. did an admirable job critically reviewing the role of early goal directed therapy in treating sepsis; by focusing on only high quality RCTs, they have found results concordant with the newer ARISE, PROMISE and PROCESS trials, and contradictory to the older Rivers study and less selective recent meta analysis. They provide a adequate review of the reasons for their results and a methodologically thorough review. I do think, however, there are extensive English revisions needed (see my annotated PDF). It also appears that the study limitations section was transplanted to the abstract rather than the discussion. Finally, some of the subgroup analyses meta-analyze two studies; a minimum of three should be included in these analyses, and they should be excluded.

The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

**VERSION 1 – AUTHOR RESPONSE**

Responses to Reviewer 1
Reviewer Name Emanuel Rivers
Institution and Country Henry Ford Hospital
Wayne State University
USA

Please leave your comments for the authors below:

The ProCESS, ARISE and ProMISE trials were not complete replications of EGDT and they acknowledged these findings. These studies essentially addressed the need for CVP monitoring in early resuscitation.

When adjusted for illness severity, all trials after EGDT reveal:

a. A significant decrease in mortality, equivalency, and no harm compared to EGDT.

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b. Lactate screening and antibiotics were standard care prior to enrollment and required, not in the EGDT study.

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Enrollment considerations compared with the EGDT trial:

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b. APACHE II scores were lower.

c. High rates of exclusion of over 50% eligible patients.

d. Convenience enrollment during time of optimal resources.
Usual or control group care must be addressed:

a. CVC and complete compliance rates were over 50% in all treatment groups including usual care.
b. Pre-existing sepsis protocols in ProCESS, the Sepsis Six and ICU initiatives in ANZICS
c. Steroid use was present in 8-37% of patients, even before randomization.
d. Delays in RB (resuscitation bundle) compliance still improves outcomes after ICU admission.
e. Lack of blinding in all groups and studies compared to original EGDT study. This is erroneous reported in this manuscript. This is an important source of bias.
f. Rapid admission to the ICU in all trials and not an ED-based study compared to 6-8 hours in the EGDT study.

Illness severity greater in the EGDT study:

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Prospective observational studies and meta-analysis (over the last decade) number over 20,000 patients:

a. Similar baseline mortality and mortality reduction to the original EGDT.
b. Are the results of the last 3 trials representative of reality?
c. Observational trials of this size are equivalent to RCT’s.

Response to above comments:

We are grateful that you reviewed our manuscript and we consider your comments as profound suggestions to us.

The present meta-analysis aimed to pool data from high quality of RCTs and focused on whether a strict EGDT protocol combining all goals (i.e. four indicators, MAP, CVP, UO, SVO2/SCVO2) was necessary to achieve survival benefit in patients with sepsis. We found that a strict EGDT protocol in accordance with SSC guidelines showed equivalent survival benefits in patients with severe sepsis or septic shock compared with other protocols.

However, the pooled results need to be viewed cautiously because of following reasons:

First, the study cohort of Rivers was slightly older than those in three recent studies. Also, higher rates of chronic coexisting health condition, higher initial serum lactate level and lower ScvO2 level were found in the study population of Rivers et al.’ study, and the APACHE II score was relatively lower in three recent trials.

Second, the mortality in all groups of recent three trials was much lower than that in Rivers et al. study, which may result from rapid recognition and management of severe sepsis patients and aggressive intravenous fluids and antibiotics treatment prior to enrollment in these studies, rendering the effect of EGDT underpowered.

Third, rapid and effective resuscitation of sepsis with modified clinician behaviors following the SSC guidelines led to the progressive decrease in sepsis mortality over the last decades.

It is worth mentioning that the results of current meta-analysis and recent three trials did not undermine the effect of EGDT. Instead, it urged us to find a more practical and cost-saving approach that could yield similar survival outcomes. Given that we were uncertain of which element of EGDT is more closely related to the reduction of mortality, further well-designed studies are still warranted to find a more practical and simplified protocol.

P.S. Response to e. Lack of blinding in all groups and studies compared to original EGDT study. This is erroneous reported in this manuscript. This is an important source of bias.

We have corrected the error about the blinding assessment. River et al reported that physicians were unaware of the patients’ study-group assignments, so they followed the rule of blinding while the rest four trials failed.

No Kappa (inter-rater agreement) coefficient to support their screening and inclusion process.
Response: The Kappa coefficient is 83.2% for Hong Yu and Dongmei Chi, 76.7% for Hong Yu and Siyang Wang and 94% for Dongmei Chi and Siyang Wang.

There is no published protocol in the usual care groups. As PRISMA statement refers Without a protocol that is publicly accessible, it is difficult to judge between appropriate and inappropriate modifications on statistical analysis and eligibility criteria.

Response: The lack of published protocol in the usual care groups was a limitation in our manuscript. However, the present meta-analysis focused on whether a strict EGDT protocol combining all goals was necessary to achieve survival benefit in patients with sepsis. We compared a strict EGDT protocol with a non-EGDT protocol. In this article, we cannot confirm which element of EGDT is more closely related to the reduction on mortality, so further well-designed studies are still warranted to find a more practical and simplified approach.

Assess the confidence on their estimate using the GRADE approach of their estimates is showing
a. adequate quality of evidence
b. High heterogeneity
c. High indirectness (high differences between control groups mortality between Rivers and harmonized trials)
d. high Imprecision (based on their 95% confidence interval estimates EGDT could provide a 40% reduction in mortality or increase mortality by 7%), even when the largest portion of the meta analysis favor EGDT they comment that there are differences in mortality
e. Unable to evaluate publication bias but they failed to provide gray literature and search for unpublished data.

Response: GRADE system grades of evidence are very low for 28-day mortality, moderate for 60-day mortality, and 90-day mortality (see Appendix 2).

Response for e: The publication bias was not assessed because of the limit of the amount of included studies. We have searched on ClinicalTrials.gov and the System for Information on Grey Literature for unpublished data and gray literature, respectively. There are 13 potentially relevant articles. None of them was included in this meta-analysis.

Responses to Reviewer 2
Reviewer Name John C. O'Horo
Institution and Country Mayo Clinic
Rochester, MN
United States

Please leave your comments for the authors below:
Yu et al. did an admirable job critically reviewing the role of early goal directed therapy in treating sepsis; by focusing on only high quality RCTs, they have found results concordant with the newer ARISE, PROMISE and PROCESS trials, and contradictory to the older Rivers study and less selective recent meta analysis. They provide an adequate review of the reasons for their results and a methodologically thorough review.

I do think, however, there are extensive English revisions needed (see my annotated PDF).

Response: The manuscript has been sent to a native English speaker to correct and improve English usage to meet the high standards of BMJ Open. There are some responses to the annotation in PDF as follows:
a) We eliminate the vague key word “usual care”.
b) The trial of Rivers et al. was a single center study, so we cannot delete the “SC-single center”.
c) We explained the source of heterogeneity in discussion section (page23, line 1-4)

It also appears that the study limitations section was transplanted to the abstract rather than the discussion.

Response: The limitations section was available both in discussion section and after abstract section.
The instructions for authors of BMJ Open command authors to place the 'Article summary' section consisting of the heading: 'Strengths and limitations of this study' after the abstract.

Finally, some of the subgroup analyses meta-analyze two studies; a minimum of three should be included in these analyses, and they should be excluded.

Response: We have excluded outcomes whose data were available in less than three trials. So, secondary outcomes that focus on duration of hospital stay, APACHE II score and use of organ support (cardiovascular, respiratory and renal system) were analyzed in this revised version.

**GENERAL COMMENTS**

The authors are comparing studies that have different methodologies, patient populations and conducted in different eras. These make a broad conclusion difficult as many of these differences are in conflict with PRISIM.

Furthermore, the intent of this meta-analysis is to identify which component is essential thus decreasing the need for a "protocol" of a simpler protocol. Anytime one treats a patient, there are steps in care which is protocol. These studies are essentially a play on words rather than an investigation. When treating an acute myocardial infarction, stroke of trauma patient, what is wrong with a protocol or a standardized or reproducible series of actions?

A meta-analysis assumes that patient populations are homogeneous and thus the results of studies investigating an intervention are valid. The problem with this meta-analysis of EGDT is that there is significant hemodynamic heterogeneity in these enrolled patient populations. The fluid challenge was 1 liter vs. 20-30 ml/kg yielding a different hemodynamic phenotype of less illness severity.

What is protocolized care? Because patient care is done in an orderly fashion, using the word "protocolized" seems to be the basis of characterizing a study. The ProCESS, ARISE and ProMISE protocolized the following important components of EGDT and called it usual care: Screening risk stratification using SIRS, Fluid challenge, Lactate screening for cryptic shock and early antibiotic administration. This is a protocol.

National limits on ED length of stay (Australia and United Kingdom) were in place during these studies conduction. The UK used a sepsis six protocol before and during the ProMISE trial conduction. There were also national sepsis initiatives in the UK during the trials conduction. This was a protocol.

These trio of trials were conducted 7-8 years after the EGDT (2008-2015) with a trial conduction duration ranging between 4 to 8 years while SSC guidelines were published in 2004, 2008, and 2012. Multiple studies have shown that sepsis mortality has decreased over 50% during this time period. There should be an adjustment for these factors.

There are numerous methodological differences that should be examining before applying PRISMA.
In EGDT study care was blinded to the ICU clinicians the trio of trials were unblinded. The trio trials were performed in ICU rather than ED. Trilogy duration of the ED stay less than 3 hours vs. 6-8 hours in EGDT.

Illness severity as patients with acute pulmonary edema (ALI) excluded in the trio and mechanical ventilation rates (54% in EGDT vs. 26% in the trio). These patients are of different illness severity.

Sudden cardiopulmonary were diminished by 50% as a result of screening in the EGDT study. This was not mentioned in the trio of trials. This reduced mortality but were not examined.

Steroid use in 8-37% of patients, none in EGDT. How is this adjusted for as steroids have associated with improved mortality?

Even providing delayed resuscitation bundle completion after 6 hours of study improves outcomes.

What if the trio of trials:
Examined patients with a low ScvO2 at baseline?
Excluded patients with a central line placement in the control groups?
Adjusted for non-blinding?
Adjusted for changes in sepsis mortality over the last decade?
Adjusted for steroid use?
Adjusted for cross over care (EGDT) before CVP placement?

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1
Emanuel Rivers
Henry Ford Hospital, Wayne State University, USA

The authors are comparing studies that have different methodologies, patient populations and conducted in different eras. These make a broad conclusion difficult as many of these differences are in conflict with PRISMA.

Response:
Thanks a lot for your helpful suggestion. We have now modified the DISCUSSION sections (See Page21, details in following responses) to clarify the differences between enrolled studies, including illness severity, methodologies and study eras, which should be taken into consideration when we viewed the results of this meta-analysis.

A meta-analysis assumes that patient populations are homogeneous and thus the results of studies investigating an intervention are valid. The problem with this meta-analysis of EGDT is that there is significant hemodynamic heterogeneity in these enrolled populations. The fluid challenge was 1 liter vs. 20-30 ml/kg yielding a different hemodynamic phenotype of less illness severity.

Illness severity as patients with acute pulmonary edema (ALI) excluded in the trio and mechanical ventilation rates (54% in EGDT vs. 26% in the trio). These patients are of different illness severity.

Response:
Indeed, the pooled results need to be viewed cautiously because the study cohorts between these trio
of trials and Rivers et al. were of different illness severity. We have now modified the DISCUSSION sections (See Page21). We have added “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 versus 1000 ml), which yields a hemodynamic heterogeneity in these enrolled studies.” and “Also, higher rates of chronic coexisting health condition, higher initial serum lactate levels and lower ScvO2 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”.

Furthermore, the intent of this meta-analysis is to identify which component is essential thus decreasing the need for a "protocol" of a simpler protocol. Anytime one treats a patient, there are steps in care which is protocol. These studies are essentially a play on words rather than an investigation. When treating an acute myocardial infarction, stroke of trauma patient, what is wrong with a protocol or a standardized or reproducible series of actions?

What is protocolized care? Because patient care is done in an orderly fashion, using the word "protocolized" seems to be the basis of characterizing a study. The ProCESS, ARISE and ProMISe protocolized the following important components of EGDT and called it usual care: Screening risk stratification using SIRS, Fluid challenge, Lactate screening for cryptic shock and early antibiotic administration. This is a protocol.

National limits on ED length of stay (Australia and United Kingdom) were in place during these studies conduction. The UK used a sepsis six protocol before and during the ProMISE trial conduction. There were also national sepsis initiatives in the UK during the trials conduction. This was a protocol.

These trio of trials were conducted 7-8 years after the EGDT (2008-2015) with a trial conduction duration ranging between 4 to 8 years while SSC guidelines were published in 2004, 2008, and 2012. Multiple studies have shown that sepsis mortality has decreased over 50% during this time period. There should be an adjustment for these factors.

Response:
We agreed the therapeutic effect of EGDT and aimed at finding whether a strict EGDT protocol combining all goals was necessary to achieve survival benefit in patients with sepsis. In our manuscript, we emphasize that the pooled results need to be viewed cautiously, because of the ambiguous and vague concept of "usual care” and significant change of "usual care” for sepsis over the decade due to the influence of EGDT concept of Rivers et al.. We have now modified the DISCUSSION sections (See Page22) and we have added “It is worth mentioning that the treatments made by the treating clinical team in the usual care group were not reported in detail in the trio of trials, and it is rational to assume that usual care has changed dramatically due to the influence of EGDT concept of Rivers et al.. It is evidenced by the progressive decrease in sepsis mortality over the last decade. Also, the trio of trials were conducted with a duration ranging between 4 to 8 years, during which period the SSC Guidelines recommending EGDT protocol updated in 2008 (later updated in 2012), and the United Kingdom used a sepsis six protocol before and during the ProMISE trial conduction. Which is more important is that even in the usual care group, the central venous catheterization (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 [10-12]. Hence, the rapid and effective resuscitation in management of sepsis patients with modified clinician behaviors in the usual care group might render the effect of EGDT underpowered”.

There are numerous methodological differences that should be examining before applying PRISMA.

In EGDT study care was blinded to the ICU clinicians the trio of trials were unblinded. The trio trials were performed in ICU rather than ED. Trilogy duration of the ED stay less than 3 hours vs. 6-8 hours
in EGDT.

Steroid use in 8-37% of patients, none in EGDT. How is this adjusted for as steroids have associated with improved mortality?

Response:
We have now modified the DISCUSSION sections (See Page21) to clarify the methodological differences between included studies. We have added “Secondly, there are some methodological differences that should be examined before viewing the results. In Rivers et al study patient care was blinded to the ICU clinicians while the rest trials were unblinded. Corticosteroid was administrated in 8-37% of patients in the trio of trials, but not in Rivers et al, which might be associated with improved mortality in the recent three trials, as it was reported that corticosteroid therapy showed significant shock reversal effect and improved mortality in vasopressor-unresponsive patients with septic shock”. Sudden cardiopulmonary events were diminished by 50% as a result of screening in the EGDT study. It may reduce mortality but this was not mentioned in the trio of trials. This reduced mortality but were not examined.

Response:
We have now modified the DISCUSSION sections (See the end of Page21). We have added “Also, the recent three trials did not compare the causes of death between two groups, especially the rate of that due to sudden cardiovascular collapse. Rivers et al. assumed that sudden cardiovascular collapse was an important cause of early death and the EGDT benefits arose from early identification of cardiovascular collapse”.

Even providing delayed resuscitation bundle completion after 6 hours of study improves outcomes.

Response:
In our manuscript, we focused on an early 6 hours of resuscitation recommended by SSC guideline. Hence, we did not involve the delayed resuscitation in our DISCUSSION section.

What if the trio of trials:
Examined patients with a low ScvO2 at baseline?
Excluded patients with a central line placement in the control groups?
Adjusted for non-blinding?
Adjusted for changes in sepsis mortality over the last decade?
Adjusted for steroid use?
Adjusted for cross over care (EGDT) before CVP placement?

Response:
If we can rule out the heterogeneity between these trials, the results would be more valid. Therefore, in DISCUSSION section, we discussed the difference in patient populations, study design and dramatical change in usual care and improved mortality over the decades, which enlightened us to understand the results of this meta-analysis better.

VERSION 3 - REVIEW

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| REVIEW RETURNED | 26-Dec-2015 |
| GENERAL COMMENTS | Randomized trials in the attempt to replicate or imitate previous trials many times lose relevance because of factors affecting trial conduction and results. These trials may be bias from the start unless one examines the trials conduction. If one changes the patient population, and methodology, differences in results may occur from the original trial no matter how well conducted. A more granular look at the conduction of these trials compared to EGDT using the principles of PRISMA would be of interest to the reader.

The definition of a well conducted trial
In a double blinded randomized control trial, the control and treatment groups are well defined and receive distinctly different treatments in a blinded fashion. The trio of trials (ProCESS, ARISE and ProMISE) were conducted with therapy that was unblinded. There was also a cross over between of treatment between the control and treatment groups. When the rigors of PRISM are applied for a meta-analysis, an appropriate adjustment for this bias is required for an appropriate conclusion.

What is usual care or control group care?
The majority of sites in the ProCESS trial had pre-existing sepsis protocols (containing EGDT) accessible online before and during enrollment which means that the control group (usual care) has significant resemblance to the treatment group. In addition to SSC, parallel initiatives in the ProMISE trial (Sepsis Six) National limits on ED length of stay (Australia and United Kingdom) were in place during these studies conduction [1, 2]. This bias obviously diminishes the treatment effect between groups leading to a negative trial [3, 4]. This does not mean that EGDT is not effective or debatable. How was this bias examined and adjusted for using PRISM.

How can the an undefined treatment be examined in a meta-analysis?

What is protocololized care?
The trio of trials report an all time low sepsis mortality on each continent using some standard of care. This is actually a confirmation of the original EGDT trial. Early screening using SIRS, risk stratification using lactate, cultures, antibiotics and ICU admission within 3 hours was performed in all treatment groups and thus represent a form of protocolized care. The real issue is whether a central venous catheter (CVC) needs to be performed in all patients during the early management of severe sepsis and septic shock. However, over 50% of all groups got CVP lines placed. The trio of trials should examine the data with these patient excluded to determine if there is a mortality benefit.

Discussion
The authors do an excellent job of bringing out critical differences in the discussion between EGDT and the trio of trials. However, what statistical procedures were performed to examine these sources of bias using PRISMA? As these issues so critical that it limits the conclusion of these trials.

A table should be made to itemize all these issues and differences between studies and the potential source of bias. This is important in the methodology of PRISMA and for the reader to understand the conclusions of this meta-analysis.

1. Daniels R, Nutbeam T, McNamara G, Galvin C: The sepsis six

**VERSION 3 – AUTHOR RESPONSE**

Reviewer: 1
Emanuel Rivers
Henry Ford Hospital, Wayne State University, USA

Comments:
Randomized trials in the attempt to replicate or imitate previous trials many times lose relevance because of factors affecting trial conduction and results. These trials may be bias from the start unless one examines the trials conduction. If one changes the patient population, and methodology, differences in results may occur from the original trial no matter how well conducted. A more granular look at the conduction of these trials compared to EGDT using the principles of PRISMA would be of interest to the reader.

The definition of a well conducted trial
In a double blinded randomized control trial, the control and treatment groups are well defined and receive distinctly different treatments in a blinded fashion. The trio of trials (ProCESS, ARISE and ProMISE) were conducted with therapy that was unblinded. There was also a cross over between of treatment between the control and treatment groups. When the rigors of PRISMA are applied for a meta-analysis, an appropriate adjustment for this bias is required for an appropriate conclusion.

What is usual care or control group care?
The majority of sites in the ProCESS trial had pre-existing sepsis protocols (containing EGDT) accessible online before and during enrollment which means that the control group (usual care) has significant resemblance to the treatment group.
In addition to SSC, parallel initiatives in the ProMISE trial (Sepsis Six) National limits on ED length of stay (Australia and United Kingdom) were in place during these studies conduction [1, 2]. This bias obviously diminishes the treatment effect between groups leading to a negative trial [3, 4]. This does not mean that EGDT is not effective or debatable. How was this bias examined and adjusted for using PRISMA. How can the undefined treatment be examined in a meta-analysis?

Response:
Indeed, the undefined treatment in the usual care group in the three negative trials may bias the results of the meta-analysis, as the potential confounding of cross over of treatment between two groups and modified clinician behaviors in the usual care group after recommendation of EGDT in SSC guidelines. However, the bias cannot be easily ruled out using PRISMA, so we clarify the bias in the DISCUSSION sections (See Page22 line8) “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 cross over of treatment between two groups. Also, it is rational to assume that the usual care has changed dramatically due to the influence of the Rivers et al trial advocating EGDT. It is evidenced by the progressive decrease in sepsis mortality over the last decade. Also, the
trio of trials were conducted with a duration ranging between 4 to 8 years, during which period the SSC Guidelines recommending EGDT protocol updated in 2008 (later updated in 2012), and the United Kingdom used a sepsis six protocol before and during the ProMISE trial conduction. Which is more important is that even in the usual care group, the central venous catheterization (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. Hence, the cross over of treatment between two groups and rapid and effective resuscitation in management of sepsis patients with modified clinician behaviors in the usual care group might render the effect of EGDT underpowered.”

Comments:
What is protocolized care?
The trio of trials report an all time low sepsis mortality on each continent using some standard of care. This is actually a confirmation of the original EGDT trial. Early screening using SIRS, risk stratification using lactate, cultures, antibiotics and ICU admission within 3 hours was performed in all treatment groups and thus represent a form of protocolized care. The real issue is whether a central venous catheter (CVC) needs to be performed in all patients during the early management of severe sepsis and septic shock. However, over 50% of all groups got CVP lines placed. The trio of trials should examine the data with these patient excluded to determine if there is a mortality benefit.

Response:
We have now modified the DISCUSSION sections (See Page23 line6) “Because of lack of high-level evidence of validation of EGDT replicating Rivers et al trial, the trio of trials designed multi-center RCTs. However, potential confounding of recruiting milder patients, more aggressive antibiotic therapy and cross over 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.”

Comments:
Discussion
The authors do an excellent job of bringing out critical differences in the discussion between EGDT and the trio of trials. However, what statistical procedures were performed to examine these sources of bias using PRISMA? As these issues so critical that it limits the conclusion of these trials.

Response:
According to methodology of PRISMA, the statistical procedures including:

a) Risk of bias individual studies---See Figure2
b) Homogeneity assumption---For primary outcome, 28-day mortality (I2=71%); 60-day mortality (I2=43%); 90-day mortality (I2=0%),
c) sensitivity or subgroup analyses---See Appendix2
d) publication bias---None (The publication bias was not assessed on the account of the limited of the amount of included studies)
e) GRADE summary---See Appendix3

Comments:
A table should be made to itemize all these issues and differences between studies and the potential source of bias. This is important in the methodology of PRISMA and for the reader to understand the conclusions of this meta-analysis.

Response:
We added “Table 2 The source of bias in terms of patient population and methodology of included trials” in the DISCUSSION sections (See Page21).
We have now modified the CONCLUSION sections as follows:

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.

GENERAL COMMENTS

The authors have done an excellent job in making the changes and corrections in the manuscript. A recent article by Burrell et al reviews an ongoing sepsis initiative during conduction (2009-2913) of the ARISE trial in New South Wales [1]. This was associated with a mortality reduction from 19.3 to 14.1% absolute or a 25% relative mortality reduction. Evidence of improved sepsis care exist in ProCESS (50% of the centers had SSC protocols), ProMISE (Sepsis Six) and ARISE trials (Sepsis Six) [2-4]. This decreases the treatment effect in all groups, diminishes the power and increases the probability of a negative trial. This occurs in spite of being 3 large randomized control trials of “high quality”.

In this exercise to publish a meta-analysis using PRISMA, the authors have recognized a lack of blinding, decreasing mortality during study conduction, methodological differences and objective evidence of equipoise. Using PRISMA, these trials have to be adjusted for or the scientific quality adjusted because they do not reflect the original trial. If they cannot account for these factors a conclusion that EGDT is ineffective or debatable cannot be made?

With the ubiquitous changes in sepsis care over the last 15 years, how can one conduct another trial of protocolized care?

It is obvious that EGDT is effective and nothing is wrong to disagree with Angus, et al [5] as others have done with meta-analysis [6-15]. Since the publication of the EGDT trial, similar outcome benefits of the EGDT trial have been reported in over 70 observational studies comprising over 70,000 patients [2, 16-88]. It has been shown that large prospective observational studies provide an equally reliable scientific alternative to randomized control trials [17, 18, 103, 104].


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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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