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Hemodynamic goals in randomized clinical trials in patients with sepsis: a systematic review of the literature

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Abstract

Background: Patients with sepsis suffer high morbidity and mortality. We sought to conduct a systematic review of the literature to evaluate the association between hemodynamic goals of therapy and patient outcomes.

Materials and Methods: We conducted a comprehensive search of the literature to systematically review hemodynamic goals used in clinical trials in patients with sepsis. We searched the literature using Pubmed (1965 – June 2006), Embase (1974-June 2006), CINAHL (1982-June 2006), pre-CINAHL, and the Cochrane Library, (2006 Issue 3) electronic databases on August 1, 2006 for the following terms: sepsis, septic shock, severe sepsis, human clinical trials. We also hand searched references and our personal files. Studies were selected if they met all of the following criteria: randomized, controlled trial study design; enrollment of adult patients with sepsis ; presence of a hemodynamic goal for patient management, > 24 h follow-up; and survival included as an outcome. Studies were independently selected and reviewed by 2 investigators.

Results: 6006 citations were retrieved, and 13 eligible articles were reviewed. MAP was a treatment goal in 9 studies and systolic blood pressure was a treatment goal in 3 studies. A goal for pulmonary artery occlusion pressure (PAOP), central venous pressure (CVP), and cardiac index (CI) was given in 4, 3 and 5 studies, respectively. The range of hemodynamic goals used in the trials were: MAP 60-100 mm Hg, CVP 6-13 mm Hg, PAOP 13-17 mm Hg, and CI 3-6 L/min/$m^{2.}$ All trials that used an SBP goal used 90 mm Hg as a goal.

Conclusions: For those trials that specify hemodynamic goals, the wide range of treatment targets suggest lack of agreement on blood pressure and filling pressure goals

for management of patients with sepsis. There was also inconsistency between trials in which measures were targeted. Further research is necessary to determine whether this lack of consistency in hemodynamic goals may contribute to heterogeneity in treatment effects for clinical trials of novel sepsis therapies.

Introduction

Standard therapy for patients with septic shock includes antibiotics, infection source control, and hemodynamic support with fluids and vasoactive medications. Despite these therapies, the mortality rate for patients with sepsis remains high at 17- 50%[1-3] . Recent advances in understanding the pathophysiology of sepsis have led to preclinical trials that attempted to modulate the inflammatory and coagulation pathways. Despite promising pathophysiological rationales derived from preclinical trials, most clinical trials of agents that were successful in preclinical trials did not demonstrate improved outcomes in patients with sepsis. It is unclear whether the failure to replicate the success of anti-sepsis agents seen in preclinical trials was due to the agents tested, the hemodynamic goals of therapy chosen, or the failure of preclinical models to reflect clinical infections.

The Surviving Sepsis Campaign published guidelines for the hemodynamic support of patients with sepsis[4] . However, these recommendations for treatment are based primarily on expert opinion, small non –randomized trials and short-term trials primarily aimed at demonstrating physiological principles. Hemodynamic goals vary widely among hospitals. Little is known about variation in hemodynamic goals in clinical trials and whether this variation is associated with patient outcomes. To better understand the hemodynamic goals in clinical trials in the sepsis research, and to inform future research into anti-sepsis agents, we performed a systematic review of the literature.

Methods

Study Selection Criteria

Studies eligible for this review met the following criteria: randomized, controlled trial study design; enrollment of adult patients with sepsis ; presence of a hemodynamic goal for patient management, > 24 h follow-up; and survival included as an outcome. The last two requirements served to eliminate studies that were exclusively designed to measure organ function over a limited time period since this endpoint may be an inadequate surrogate for mortality in trials of novel sepsis therapies [5, 6]

Search Strategy

We conducted a comprehensive search of the literature using Medline from January 1, 1965 to June 1, 2006 and the following medical subject heading (MeSH) terms: sepsis OR severe sepsis OR septic shock AND human clinical trials. Using similar terms, we also searched Embase (1974-June 2006), CINAHL (1982-June 2006), pre-CINAHL, and the Cochrane Library (2006 Issue 3) electronic databases on August 1, 2006. We hand searched references of relevant review articles[4, 5, 7] and our personal files.

Study Selection

Two investigators (JES, SN) independently reviewed citations based on the selection criteria. The abstracts of all citations selected by either investigator, and the full text article for all eligible abstracts were independently reviewed by two investigators (JES and GS). Agreement between reviewers was calculated by both percentage agreement and kappa statistics. Disagreement regarding eligibility was resolved by consensus.

Data Extraction, Synthesis and Study Quality

For each eligible full text article, two authors (JES, GS) independently abstracted measures of patient baseline characteristics, duration of trial and mortality rates. To summarize the hemodynamic goals of each trial, both measure(s) of blood pressure and/or filling pressure used and/or cardiac index, and the target range for each measure, were abstracted for each trial. We evaluated study quality according to the following criteria: (1) appropriate patient selection: identification of sepsis using accepted diagnostic criteria[8] , (2) control for co-interventions: standardized protocol for volume resuscitation prior to initiating vasopressors, and (3) appropriate analysis using the criteria proposed by Jadad et al[9]. We used these criteria to comment on the methodological quality of studies, but did not exclude studies from the review based on this evaluation. Since the trials tested the efficacy of different sepsis agents and used different outcome measures, we could not synthesize the effect of the therapies on patient outcomes either quantitatively or qualitatively; instead, our objective was to understand the goals used for hemodynamic management of patients across these clinical trials of sepsis.

Hemodynamic criteria

We examined the methods sections for hemodynamic treatment goals for the clinical sepsis trials. We abstracted both treatment measures (e.g. CVP, MAP) and the hemodynamic goals of treatment (e.g. CVP of 8 mm Hg). Hemodynamic measures and goals that were listed as part of the trial entry criteria, but were not included as part of a

mandated treatment strategy were excluded. We separately abstracted criteria for treatment and control groups for trials that tested specific hemodynamic endpoints. If a range of values were specified during the trial, we used the mean of the range of values specified.

Results

We identified 6006 citations from our search strategy, of which 242 abstracts and 126 full text articles were reviewed (Figure 1). Of these full text articles, 10 did not enroll sepsis patients, 5 were secondary analysis that did not include primary data and 3 were not randomized controlled trials. Of the remaining 104 studies, 76 (73%) did not include hemodynamic goals for patient management. Ultimately, 13 articles met our eligibility criteria (Table 1). Reviewer agreement on selection of eligible citations was 99% (kappa 0.79), and on selection of full-text articles was 100% (kappa =1.0).

Table 2 summarizes the measures of study quality for the eligible trials. All studies reported sepsis criteria that were based on the ACCP/SCCM consensus criteria[8] for entry into the clinical trial. Only 3 (23%) studies reported a specific protocol for volume resuscitation while 10 (76%) studies reported some measurement of organ function. Four studies (31%) met one Jadad criteria for study quality , 6 (46%) met 2 criteria and 3 (23%) met 3 criteria[9]

For blood pressure goals, 9 (69%) studies included MAP goals, with the minimum and maximum target MAP ranging from 60 to 100 (Table 1). Seven (54%) studies used MAP

goals that fell between the range of 60 to 70 mm Hg (Figure 2a) with the remaining 2 studies using 80 and 100 mm Hg[10][11]. Three (23%) studies used a systolic blood pressure goal, with all studies targeting> 90 mm Hg[10-12] . One study did not include any blood pressure goal[13]

For filling pressure goals, a central venous pressure (CVP) goal was used in 3 (23%) studies[14-16] (See Fig 2b), with target goals that ranged of 6 to 13.5 mmHg. A pulmonary artery occlusion pressures (PAOP) goal was used in 4 studies(31%), with the target ranging from 13 to 17 mm Hg[10, 12, 17, 18] (See Fig. 2c). A cardiac index goal was listed in 5 studies (38%)[12, 16, 19-21] with the target ranging from 3 to 6 L/min/m^2(Fig 2d). One study used separate hemodynamic goals for the treatment and control arms[12]. One study specified oxygen delivery goals[18] . In all, 8 (61%) studies required a pulmonary artery catheter as part of the study procedures. Of note, 1 study that required the use of a PA catheter as part of the protocol did not specify treatment goals that would require the use of the catheter[11].

Three studies in this study were designed to test specific hemodynamic treatment paradigms. Rivers and colleagues demonstrated that early goal-directed therapy over a 6 hour period resulted in a 12.6 absolute decrease in 60-day mortality for patients with severe sepsis[14] . Alia and colleagues examined the role of goal-directed therapy in patients with established severe sepsis and septic shock[18] , and Tuchschmidt and colleagues examined the role of goal directed therapy in septic shock[12] . Both Alia and Tuchschmidt included a treatment arm that specified supranormal therapeutic goals[12,

18]. The other 10 studies incorporated specific hemodynamic goals into trials of novel therapies specifically directed at the pathophysiology of sepsis. Analysis of the studies excluding the 2 trials that include supranormal therapeutic goals does not alter the variability in treatment goals seen in this study, with the exception of a narrowed cardiac index range (data not shown)

Discussion

This systematic review of hemodynamic goals in sepsis clinical trials has two major findings. First, of the 126 clinical studies that were reviewed in full, 73% did not include hemodynamic goals of therapy. Of those 13 studies that met our inclusion criteria, there was a wide range of targeted hemodynamic goals and measures. Importantly, not all studies included similar targets or measures.

Most of the studies used MAP as their hemodynamic measure for directing sepsis therapy. Only 3 of the studies used a systolic blood pressure as a measure, with all 3 selecting 90 mm Hg as the target [10-12]. While the ACCP/SCCM consensus definition uses systolic blood pressure as a marker of hypotension[8] , some experts suggest that MAP may be more closely associated with organ perfusion[22] . The choice of different measures in these studies may reflect variation in practice between clinicians in blood pressure targets for patients with sepsis

In 2 of studies, the MAP goal was higher than in the other studies. First, in a trial of a non-specific nitric oxide synthase inhibitor, the target MAP was between 70 and 90 mm

Hg with an actual mean MAP of 86 mmHg achieved in both the treatment and control groups[21] . This trial was the first sepsis trial to demonstrate a statistically significant result, with an increase in the mortality rate for the treatment (vs. placebo) group. Second, a trial of a chimeric monoclonal antibody to TNF-α targeted a MAP of between 90 and 110mm Hg[23] . In this trial there was no difference in mortality rates between study groups. The differing results in the these two trials may have been caused by differing sample sizes of the trials, differing agents used, or other unmeasured co-interventions. Achieving a higher MAP may lower cardiac output, oxygen delivery and regional perfusion, thus modifying the effects of sepsis therapies.

Only 54% of the studies provided a filling pressure goal as part of the treatment regimen. 3 studies mandated CVP goals while 4 mandated a PAOP goal. Adequate volume resuscitation is an essential part of hemodynamic management. While some recent studies have cast doubt on whether the PAOP represents an adequate surrogate for left ventricular end diastolic volume, or whether use of the PA catheter can improve outcomes in patients with sepsis[24, 25] , the wide range of treatment goals and measures here, and the absence of a filling pressure goal in the majority of studies suggests heterogeneity in thought as to filling pressure targets in patients with sepsis. Similar heterogeneity is seen in the cardiac index goals in the studies that included such goals.

Given the past and present interest in goal-directed therapy for patients with sepsis, we had hypothesized that a greater number of studies would be eligible for this review. Rivers and colleagues demonstrated that early goal-directed therapy over a 6 hour period for patients with severe sepsis started in the emergency room improved outcomes[14] . It

is notable that this study, in contrast to previous studies, used central venous oxygen saturation as compared to the cardiac output and mixed venous oxygen saturation measurements. However, many of these studies that did not meet our inclusion criteria enrolled patients who did not have sepsis, but only were at risk for it[26] . Furthermore, only a few studies of specific agents aimed at modulating the inflammatory cascade included specific hemodynamic goals. It is noteworthy that the 4 largest clinical studies evaluating novel therapies in patients with sepsis, evaluating drotrecogin alpha , tissue factor pathway inhibitor, antithrombin III , and monoclonal antibodies to TNF[27-30], did not specify hemodynamic goals.

Only 3 studies included specific fluid challenge as part of their protocol[10, 12, 14]. All 3 included specific volume challenge boluses to reach a desired filling pressure, but all included different fluid dosing and filling pressure goals. Adequate volume resuscitation remains a key component in the treatment of septic patients. While filling pressure may represent on measure of the adequacy of resuscitation, a recent report suggests that filling pressure goals alone do not correlate well with changes in stroke volume index [31]

This systematic review has several potential limitations. First, the heterogeneity of populations and therapies prevent synthesis of findings regarding the hemodynamic goals on treatment outcomes It may not be possible to generalize information about treatment paradigms across these differing studies with agents with variable mechanisms of actions. However, the variation in treatment goals seen across these studies provides evidence that practice patterns remain heterogeneous in the provision of hemodynamic support. In

recent years standardized treatment protocols have been implemented in critically ill populations including include standard ventilatory weaning methods[32], protocolized ventilatory strategies for patients with acute lung injury[33, 34], and insulin therapy goals[35, 36] . Yet broad use of protocols to achieve hemodynamic goals in patients with sepsis remains elusive.

Second, we did not include studies of patients who were at risk for developing sepsis. Thus, we cannot extrapolate from our findings to the general critically ill population. It is possible that those studies of the "at risk population" would lead to important information about the use of hemodynamic goals in critically ill populations. However, our study does provide information on those patients with established sepsis. We chose to focus on patients with sepsis since adequate supportive care with fluid and vasopressors remains one of the main tenets of therapy for patients with sepsis.

The wide range of hemodynamic goals in the selected studies underscores the lack of convincing data to support one hemodynamic goal over another, but raises the possibility that these goals may modify treatment effects of specific agents. Hemodynamic therapy is a vital portion of the treatment strategy, and it remains biologically plausible that agents that effect blood pressure and cardiac output may modify the effects of specific anti-sepsis agents. Choice of vasopressor agents for patients with septic shock may also modify the effects of such anti-sepsis agents.

The lack of specific hemodynamic measures and goals observed in this systematic review may reflect the variation in clinicians' general beliefs and practice, or differences in patient populations studied. However, the heterogenous patient population that develops sepsis (e.g., elderly patient with urosepsis, young trauma patient with intra-abdominal sepsis, brain injured patient with ventilated-acquired pneumonia) may preclude the use of a single hemodynamic goal for all septic patients. The recently published surviving sepsis campaign guidelines do give basic guidelines for resuscitation goals, but suggest that the treatment goals may be individualized based on patient response to therapy[4]

Conclusions

Fewer than 30% of all clinical trials in the field of sepsis have mandated hemodynamic treatment goals for patient management. For those studies that do report hemodynamic goals of therapy, there are wide variation in measures followed and goals chosen. If hemodynamic goals are related to outcomes and to specific agents, the variation in hemodynamic goals may introduce bias into clinical trials in sepsis patients. Further research is needed to determine whether standardization of measures and target goals for hemodynamic monitoring may improve clinical research in the field of sepsis.

Key Messages

- Most sepsis clinical trials reviewed did not include hemodynamic goals of therapy. Of, note the 4 largest clinical trials evaluating novel therapies in patients with sepsis did not specify hemodynamic goals of treatment

- For those 13 studies identified in our systematic review, , there was wide variation in hemodynamic measures selected, and hemodynamic goals chosen.
- Further research is necessary to determine whether this lack of consistency in hemodynamic goals may contribute to heterogeneity in treatment effects for clinical trials of novel sepsis therapies.

Abbreviations Used

MAP- Mean Arterial Pressure
SBP- Systolic Blood Pressure
CVP – Central Venous Pressure
PAOP- Pulmonary Artery Occlusion Pressure
CI- Cardiac Index
RCT- Randomized Controlled Trial
PA Pulmonary Artery
MM- millimeter
Hg-Mercury
MeSH- Medical Subject heading

Authors' Contributions

All authors made substantial contribution to the study design and methods. JES, SN, PJP planned the study. JES, SN and GMS performed the literature review. JES, SN, DMN, SH performed the data analysis. JES drafted the manuscript and all other authors critically revised it for important intellectual content. All authors approved the final version of the manuscript for publication.

Conflicts of Interest

The authors declare they have no competing interests.

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Table 1: Study Description

	N	Year	# Centers	Study Population	Follow-up Duration for Mortality*
Tuchsmidt et al [12]	51	1992	1	Septic shock	14 days
Peake et al.[10]	20	1996	1	Septic shock	Hospital stay
Bollaert et al.[11]	40	1998	2	Septic shock	28 days
Spapen et al.[19]	22	1998	1	Septic shock	Hospital stay
Alia et al.[18]	63	1998	1	Severe Sepsis Septic shock	ICU stay
Clark et al.[23]	56	1998	1	Severe Sepsis	40 days
Boldt et al[15]	28	1999	1	Sepsis;Trauma	5 days
Briegel et al[17]	40	1999	1	Septic Shock	365 days
Rivers et al[14]	263	2001	1	Sepsis, Severe Sepsis Septic shock	60 days
Cole et al[13]	24	2002	1	Severe Sepsis Septic shock	Hospital stay
Emet et al[16]	53	2004	1	Severe Sepsis	Hospital stay
Bakker et al[20]	312	2004	48	Septic Shock	28 days
Lopez et al[21]	797	2004	128	Septic Shock	28 days

*If mortality was provided for more than one time point, the time point of the primary outcome measure was reported

Table 2. Study Treatments, Outcomes and Hemodynamic Measurements

Study	Treatment	N	Control GROUP Mortality	Study GROUP Mortality	Blood Pressure Goals	Other Hemodynamic goals
Tuchsmidt et al [12]	Elevation of Cardiac Output with Dobutamine and Fluids	51	18/25=72%	13/26=50%	SBP >90 mm Hg	Treatment: PAOP>=15 & CI >=6 L/min/M2 Control: CI>=3 L/min/M2
Peake et al[10].	N-Acetyl-Cysteine	20	5/10=50%	9/10=90%	SBP >90 mm Hg	CI >=4 L/min/m2 PAOP 15-18 mm Hg
Bollaert et al. [11]	Supraphysiologic Hydrocortisone	40	12/19=63%	7/21=32%	SBP >90 mm Hg	
Spapen et al. [19]	N-Acetyl-Cysteine	22	4/10=40%	5/12=41.6%	MAP > 65 mm Hg	CI> 4 L/min/m2
Alia et al. [18]	Maximizing of Oxygen Delivery with Dobutamine	63	21/32=65.6%	23/31=74.5%	MAP>60 mm Hg	PAOP 12-15 mm Hg Treatment DO2I> 600 ml/min/m2 Control DO2I> 330 ml/min/m2
Boldt et al[15]	Heparin	56	11/28=39.2%	10/28=35.7%	MAP > 65 mm Hg	CVP 12-15 mm Hg
Clark et al. [23]	TNF-alpha antibody	28	3/14=21.4%	3/14=21.4%	MAP90-110 mm Hg	
Briegel et al[17]	Stress Dose Hydrocortisone	40	6/20=30%	5/20=25%	MAP>70 mm Hg	PAOP 12-15 mm Hg
Rivers et al[14]	Multi-faceted Early Goal Directed Therapy Protocol	263	70/133=52.6	50/130=38.4	MAP>=65	CVP 8-12 EGDT SVO2>=70
Cole et al[13]	Continuous Hemofiltration	24	4/12=33.3%	4/12=33.3%	MAP>=70 mm Hg	
Emet et al[16]	N-Acetyl-Cysteine	53	8/26=30.7%	7/27=25.9%		CVP 4-8 mm Hg
Bakker et al[20]	Nitric Oxide Synthase Inhibitor	312	75/155=48.3%	72/155=46.2%	MAP>=70mm Hg	CI>=3 L/min/m2
Lopez et	Nitric Oxide	797	174/358=48.6%	259/439=59%	MAP 70 -90	CI>=3

al[21]	Synthase Inhibitor				mm Hg	L/min/m2

Table 3: Quality Assessment of Trials

Study	Sepsis Criteria Explicitly Stated*	Volume Challenge Explicitly Stated	JADAD SCORE Analysis
Tuchsmidt et al [12]	Y	Y**	1
Peake et al[10].	Y	Y***	2
Bollaert et al. [11]	Y	N	2
Spapen et al.[19]	Y	N	2
Alia et al.[18]	Y	N	1
Boldt et al[15]	Y	N	1
Clark et al. [23]	Y	N	3
Briegel et al[17]	Y	N	2
Rivers et al[14]	Y	Y****	3
Cole et al[13]	Y	N	1
Emet et al[16]	Y	N	2
Bakker et al[20]	Y	N	3
Lopez et al[21]	Y	N	2

*SCCM/ACCP criteria[8]
** 5% albumin in aliquots to achieve PAOP>15
*** 200 ml bolus over 15 minutes to achieve a sustained increase in PAOP>= 3 mm Hg
**** 20-30 ml/kg initial fluid bolus over 1 hour followed by 500 ml every 30 minutes to achieve CVP 8-12 mm Hg

Figure Legends

Figure 1. Study Flow Diagram. RCT indicates randomized controlled trial

Figure 2. Hemodynamic Goals in Sepsis Trials
2a. Mean Arterial Pressures (MAP) Goals in Sepsis Trials.
2b. Central Venous Pressures (CVP) Goals in Sepsis Trials.
2c. Pulmonary Artery Occlusion Pressure (PAOP) Goals in Sepsis Trials.
2d. Cardiac Index in Sepsis Trials.
For Studies that provided an interval goal range, the mean of the range is graphed. One study provided a separate cardiac index for the treatment and control groups. These are graphed separately.

Figure 1: Flow diagram of literature search results

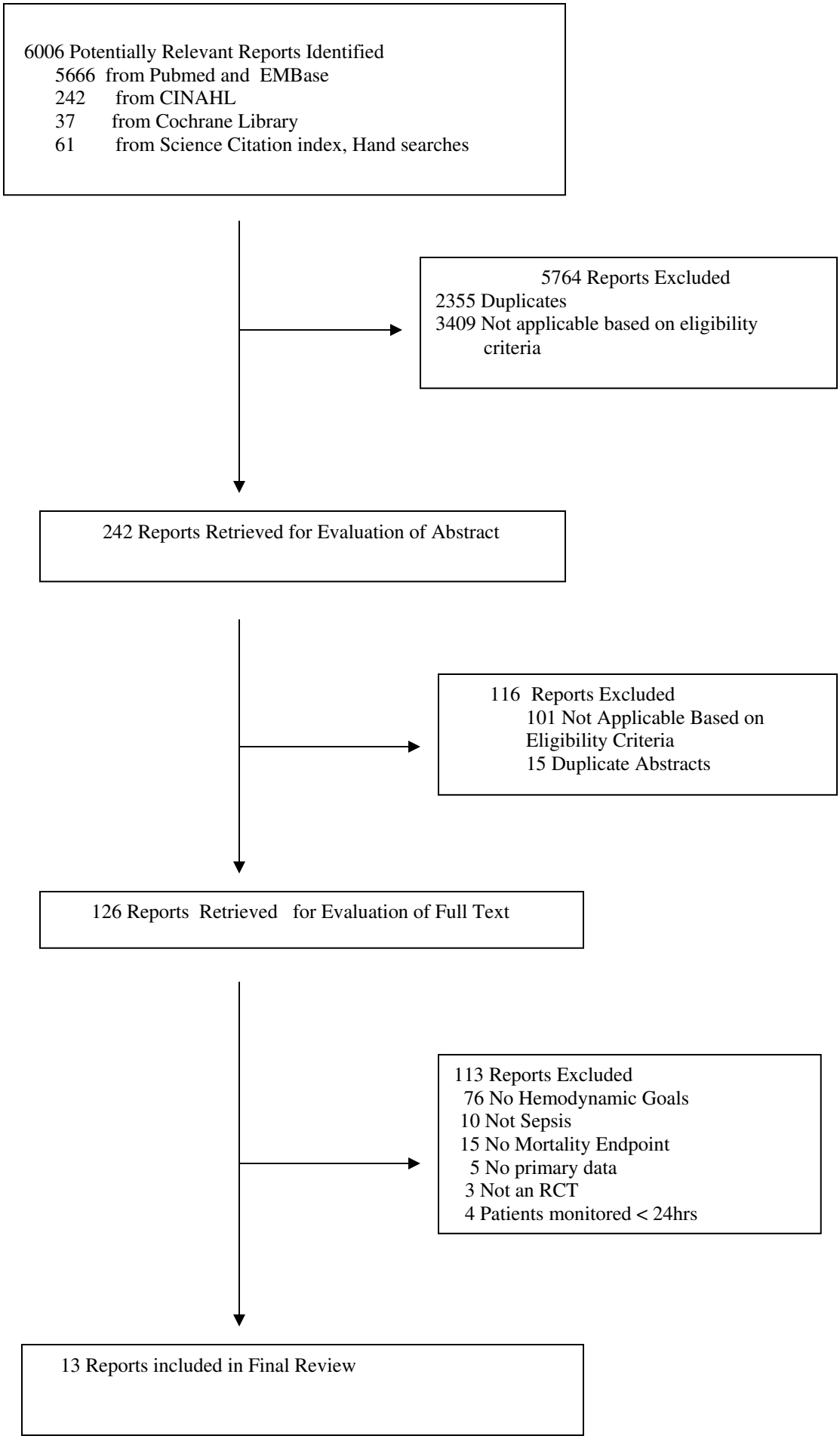
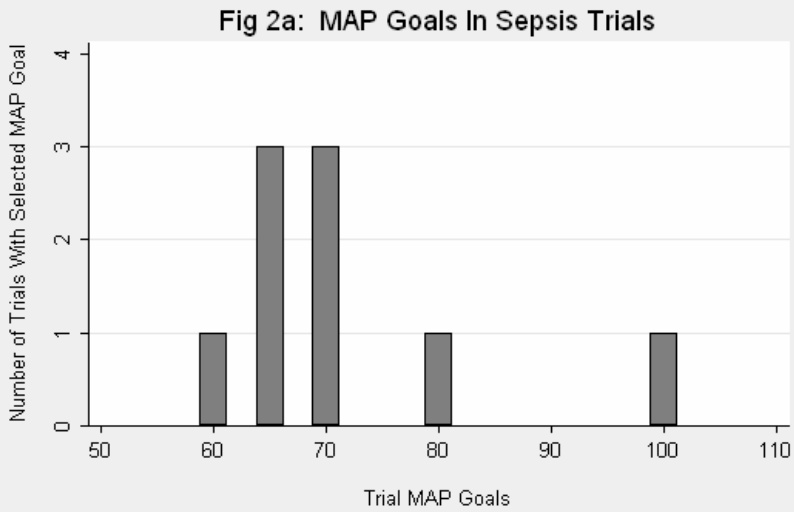
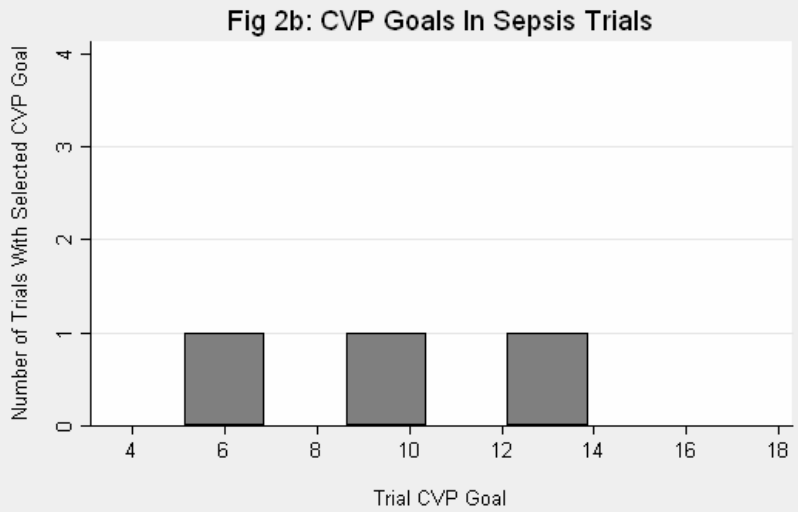


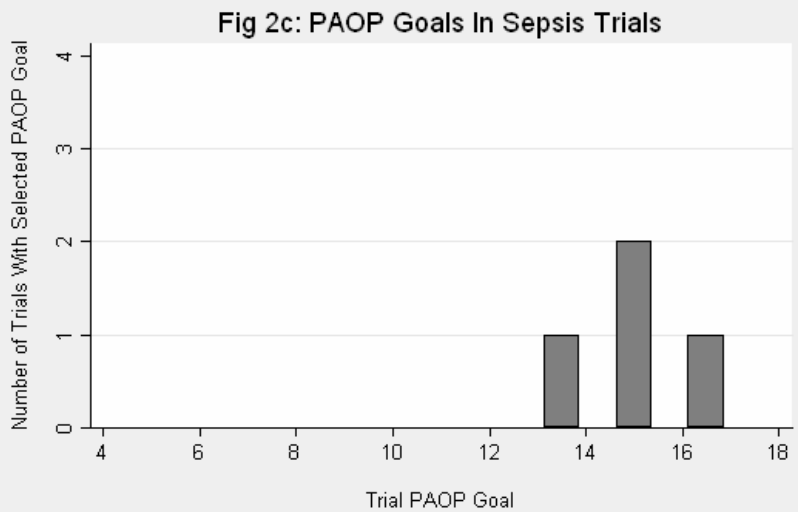
Figure 1

Figure 2

Fig 2 Hemodynamic Goals in Sepsis Trials







Additional files provided with this submission:

Additional file 1: competinginterests.doc, 37K
http://ccforum.com/imedia/1088485362147632/supp1.doc