Meta-analysis of Protocolized Goal-Directed Hemodynamic Optimization for the Management of Severe Sepsis and Septic Shock in the Emergency Department

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Introduction: To perform a meta-analysis identifying studies instituting protocolized hemodynamic optimization in the emergency department (ED) for patients with severe sepsis and septic shock.

Methods: We modeled the structure of this analysis after the QUORUM and MOOSE published recommendations for scientific reviews. A computer search to identify articles was performed from 1980 to present. Studies included for analysis were adult controlled trials implementing protocolized hemodynamic optimization in the ED for patients with severe sepsis and septic shock. Primary outcome data was extracted and analyzed by 2 reviewers with the primary endpoint being short-term mortality reported either as 28-day or in-hospital mortality.

Results: We identified 1,323 articles with 65 retrieved for review. After application of inclusion and exclusion criteria 25 studies (15 manuscripts, 10 abstracts) were included for analysis (n=9597). The mortality rate for patients receiving protocolized hemodynamic optimization (n=6031) was 25.8% contrasted to 41.6% in control groups (n=3566, $p<0.0001$).

Conclusion: Protocolized hemodynamic optimization in the ED for patients with severe sepsis and septic shock appears to reduce mortality. [West J Emerg Med. 2014;15(1):51–59.]

INTRODUCTION

The incidence of sepsis and the absolute number of sepsis-related deaths have progressively increased in the United States over the last decade, and an increasing number of critically ill patients are managed in the emergency department (ED).[1–3] An estimated 571,000 cases of severe sepsis, or roughly two-thirds of the nation's burden, present annually to an ED and spend nearly 5 hours therein.[4] Given the significant mortality associated with this patient population,[5] an important determinant of outcome is conceivably the care provided in the ED prior to intensive care unit (ICU) admission. If so, a grave responsibility rests upon ED systems to create and provide evidence-based management strategies targeting severe sepsis and septic shock.

Previous studies have examined the effect of therapeutic interventions on outcome in septic shock, such as immunotherapeutic agents, hemodynamic optimization, or pulmonary artery catheterization but have enrolled patients up to 72 hours after ICU admission.[6–9] The lack of efficacy noted in hemodynamic optimization trials, in particular, prompted editorials emphasizing that future studies target patients early in their presentation and begin intervention at a more reversible stage of organ dysfunction.[8,10–12]

Rivers et al examined whether early goal-directed therapy (EGDT) in the ED before ICU admission effectively reduces

multi-organ dysfunction and mortality rates in patients with septic shock by using specific criteria for early identification, establishing goals of resuscitation, and implementing a treatment protocol.[13] Since publication there have been other trials evaluating the impact of ED management on patients with severe sepsis and septic shock. This systematic review provides an analysis of studies instituting protocolized hemodynamic optimization for patients with severe sepsis and septic shock in the ED to determine if there is a significant reduction in mortality.

METHODS

We modeled the structure of this analysis after the QUORUM and MOOSE published recommendations for systematic scientific reviews.[14–17] A computer search to identify articles was performed by 2 investigators (KD, CW) from 1980 to December 4, 2011 using the following databases: MEDLINE, EMBASE, and CINAHL, Cochrane DSR, DARE, CCTR, and ACP Journal Club. Medical subject headings (MeSH) used were as follows: early goal-directed therapy, goal-directed therapy, goal-oriented therapy, hemodynamic optimization, sepsis bundles, supranormal oxygen delivery, sepsis oxygen delivery, resuscitation endpoints, cardiac optimization, supranormal resuscitation, mixed venous saturation, mixed central venous oxygen saturation, sepsis quality improvement, and sepsis protocol. We screened references in reviews and relevant trials to identify further pertinent articles. We performed an Internet search with the Google search-engine to identify unpublished abstracts at national and international emergency medicine and critical care conferences. And we contacted a clinical expert in the field for further assistance (JS).

Studies included for analysis were adult controlled trials implementing protocolized hemodynamic optimization in the ED for patients with severe sepsis and septic shock. Exclusion criteria were studies published prior to 1980, non-English articles, studies not reporting the outcome of short-term mortality, studies not enrolling any patients from the ED, studies excluding septic patients, preliminary studies with later manuscripts reporting the same data, and series with fewer than 10 patients. Of note, we included studies if a portion of patients were enrolled from the ED, with the remainder being enrolled from hospital floors or intensive care units. Studies were also included if the treatment protocol administered the following additional treatment interventions: activated protein C, tight glycemic control, low tidal volume ventilation, or corticosteroid administration. To reduce publication bias, we also performed a systematic search for published abstracts that had not been published in manuscript format, even though critical appraisal of such publications is limited. Our methodology was to review all published abstracts related to "sepsis" or "goal-directed therapy" in national emergency medicine (SAEM, ACEP) and critical care (SCCM, ACCP) conferences from 2001 to 2008/2010 (we searched EM national conferences through 2010, and national critical care conferences through 2008). We also included published abstracts identified as references in relevant review papers. Abstracts explicitly stating that the location of the protocolized hemodynamic optimization intervention was performed only in the ICU and not in the ED were excluded, while all others were included for analysis.

Two reviewers (CW, KD) independently applied inclusion/exclusion criteria and used a customized data-collection form and glossary of terms to systematically identify relevant trials and outcome measures. On the data collection form each recorded the primary outcome measure of short-term mortality, secondary outcome measures, and applied a level of evidence score to each study. Secondary outcome measures included: research protocol, administration of other treatments, severity of illness scores, serum lactate levels, Scv02, and hospital length of stay. Disagreements were solved by discussion. We scored articles with a methodologic quality assessment derived from prior literature.[15–18] Level 1 studies were randomized, controlled trials with all of the following criteria being fulfilled: concealed treatment allocation, similar groups at baseline, blinding to the intervention, acceptable drop-out rate, similar timing of the outcome assessment in all groups, and incorporation of an intention to treat analysis. Level 2 studies were randomized, controlled trials without >1 of the listed level 1 criteria. Level 3 studies were prospective un-randomized trials (prospective observational studies, including before/after analyses). Level 4 studies were not fully prospective, including but not limited to use of a historical or retrospective control group. Level 5 studies were published abstracts or short reports.

We used Fisher's exact test and a two tailed p-value to determine statistical significance for the primary endpoint of short-term mortality. A p-value of <0.05 was considered significant. We performed meta-analysis using Comprehensive Meta-Analysis version 2.0[19]. Odds ratios were used as effect size estimates and presented for each study along with 95% confidence intervals. Pooled estimates are presented within publication type and across all studies. The estimate of heterogeneity was moderate (i-squared=35) and was not explained by publication type, so random effect estimates are described. The random effect model assumes that the true effect size can vary from study to study and the pooled effect size is the average.

RESULTS

Database searches identified 1,323 articles (Figure 1). After combination of MeSH headings and removal of duplicates (n=614), we identified 709 articles. Six hundred forty-four articles met exclusion criteria on electronic review yielding 65 articles that were manually evaluated for clinical relevance. We identified 15controlled studies[13,20–33] fulfilling inclusion and exclusion criteria (n=3277). There was 93.3% agreement between investigators for article level-of-evidence

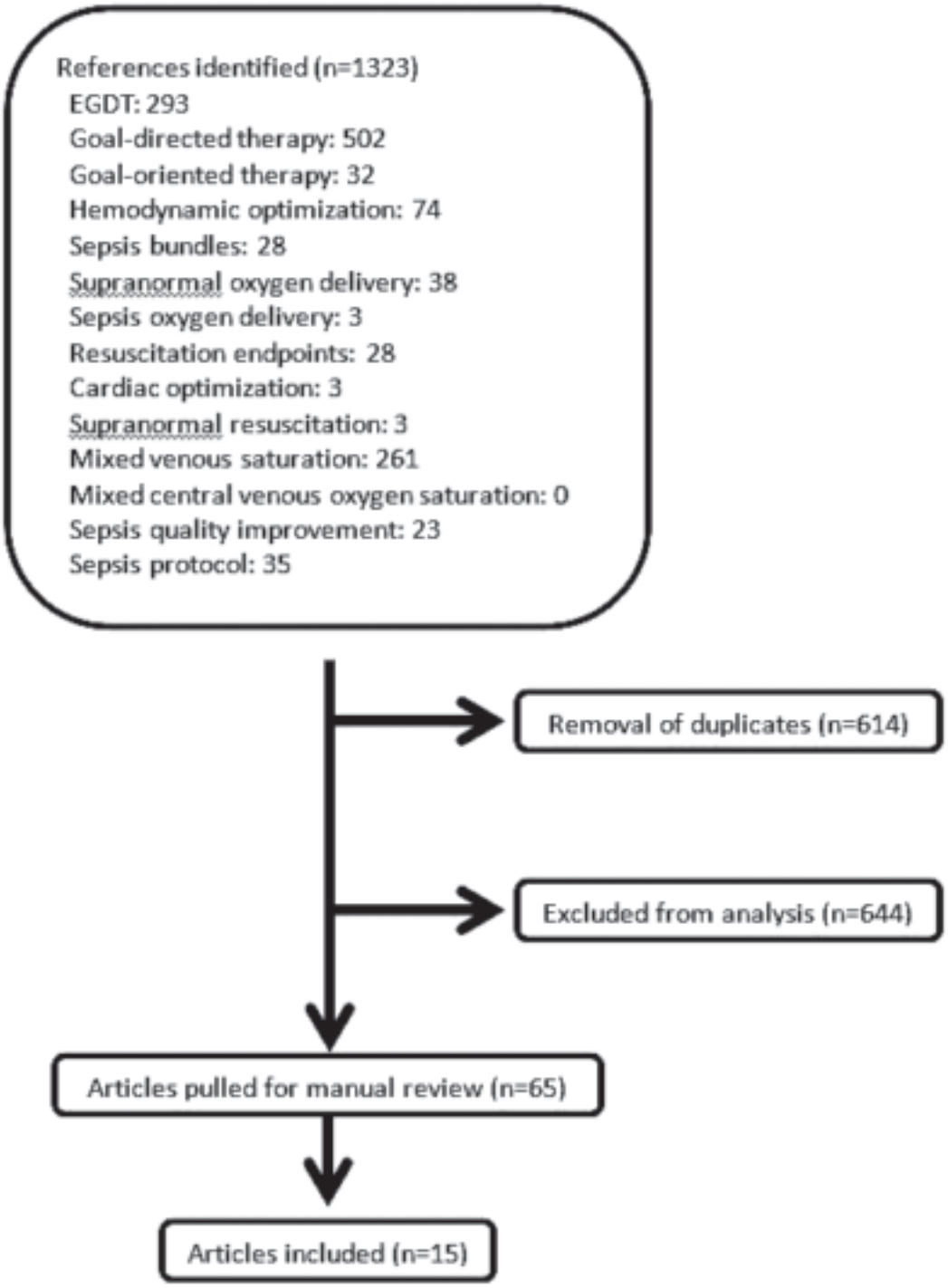

Figure 1. Flow chart of article extraction. *EGDT*, early goal-directed therapy.

scoring (Table 1), and 96.6% agreement for primary outcome data extracted from published manuscripts (Table 2). The sample size for all studies ranged from 38 to 511. An abstract search also identified 10 studies[34–43] (n=6320) with sample sizes ranging from 50 to 5,080. Cumulatively, among 25 studies and abstracts identified (n=9597) 1 study received a level 1 methodological score, 7 received a level 3 score, 7 received a level 4 score, and 10 received a level 5 score (Table 3). One study was excluded[44] because it had data reported in a later study that was included for analysis.[25]

Among published controlled studies four studies enrolled patients from both the ED (Table 2) and ICU with only one reporting the number of patients enrolled from the ED[20] (11%), while another gave a qualitative estimate[31](80%). The remaining studies (n=11) appeared to enroll patients only from the ED. Among studies reporting APACHE II scores[13,20–23,25,27,30–33] in

Table 1. Overall mortality for protocolized versus non-protocolized hemodynamic optimization for both published studies and published abstracts.

		Protocolized care mortality			Non-protocolized care mortality		
Author	N	N total	N Died	%	N total	N Died	%
Abstracts							
Gaieski, 2005	58	16	4	25	42	20	47.6
Ikeda, 2006	314	266	50	18.9	48	19	40.1
Kinsella, 2006	185	103	18	16.7	82	19	23
Mullon, 2006	196	124	43	34.5	72	29	40.3
Antro, 2006	64	36	13	36.1	28	18	64.3
Stenstrom, 2006	50	30	5	16.7	20	8	40
Armstrong, 2005	131	63	17	27	68	35	51
Tanios, 2007	96	62	17	27	34	19	55
Cannon, 2008	5080	3488	916	26.3	1592	624	39.2
Gunaga, 2008	146	48	11	23	98	37	37.8
Sub-Total	6320	4236	1094	25.8	2084	828	39.7
Manuscripts							
Rivers, 2001	263	130	38	30.5	133	59	46.5
Gao, 2005	101	52	12	23	49	24	49
Trzeciak, 2006	38	22	4	18.2	16	7	43.8
Shapiro, 2006	130	79	16	20.3	51	15	29.4
Micek, 2006	125	61	19	31.1	64	33	51.6
Jones, 2007	156	77	14	18	79	21	27
Nguyen, 2007	330	77	16	20.8	253	100	39.5
Sebat, 2007	511	426	50	11.8	85	34	40
El Sohl, 2008	174	87	34	39	87	48	55.1
Puskarich, 2009	285	206	77	37.3	79	39	49.4
Crowe, 2009	306	183	63	34.4	123	53	43.1
MacRedmond, 2010	74	37	10	27	37	19	51.4
Patel, 2010	112	59	12	20.3	53	32	61.1
Coba, 2011	498	202	75	37.1	296	140	47.3
Sivayoham, 2011	174	97	22	22.7	77	33	42.9
Sub-Total	3277	1795	462	25.7	1482	657	44.3
Total	9597	6031	1556	25.8	3566	1485	41.6

the treatment and control groups, the values were $24.8 + 6.5$ and $24.9 + 6.9$ respectively (P=0.97, paired t-test).

All studies used hemodynamic optimization pathways (Table 2) with a mean arterial pressure (MAP) threshold for vasopressors. All studies but one[20] reported mixed central venous (Scv02) or mixed venous (Sv02) oxygen saturation monitoring. All but two[32,33] had transfusion thresholds for red blood cells. In several studies, selected patients in the protocolized hemodynamic optimization group and control group were permitted to receive Activated Protein C, low tidal volume ventilation ventilation, tight glycemic control, and corticosteroids (Table 2). The mortality rate for patients receiving protocolized hemodynamic optimization (n=1795) was 25.7% contrasted to 44.3% in control groups (n=1482, $p<0.0001$, Fisher's Exact test).

Among the 10 published abstracts[34–43] identified, the mortality rate for patients receiving protocolized hemodynamic optimization (n=4236) was 25.8% contrasted to 39.7% in control groups (n=2084, $p<0.0001$, Fisher's Exact Test). Cumulatively, among all identified published studies and published abstracts (n=9597), the overall mortality rate for patients receiving protocolized hemodynamic optimization (n=6031) was 25.8% contrasted to 41.6% in control groups (n=3566, $p<0.0001$, Fisher's Exact Test). In each identified study there was a lower mortality rate in the protocolized hemodynamic optimization group compared to control groups

Table 2. Location of study and interventions performed.

Manuscript	ED only	Sv02	Early abx	Steroids	APC	Glycemic control	Vent. prot.
Rivers, 2001	X	X	X				
Gao, 2005			X	X	X	X	X
Trzeciak, 2006	X	X	X	X	X		
Shapiro, 2006	X	X	X[c]	X	X	X[a]	X
Micek, 2006	X	X	X[c]	X[b]	X		
Jones, 2007	X	X	X	X[a]	X		
Nguyen, 2007	X	X	X[ac]	X[a]	X[a]		
Sebat, 2007		X	X[c]	X	X	X	
El Sohl, 2008	X	X	X	X[a]	X	X	X
Puskarich, 2009	X	X	X	X[a]	X[a]		
Crowe, 2009	X	X	X	X			
MacRedmond, 2010	X	X	X				
Patel, 2010		X	X[c]	X	X	X	
Coba, 2011		X	X[a]	X	X	X	X
Sivayoham, 2011	X	X	X[a]				

ED, emergency department; *Abx,* antibiotics; *Sv02,* mixed venous or central venous oxygen saturation monitored; *APC,* Activated Protein C (drotrecogin alpha); *Vent Prot,* ventilation protocol
[a]Protocol group received more ($P<0.05$)
[b]Control group received more ($P<0.05$)
[c]Antibiotics administered significantly faster in protocol group ($P<0.05$)

(Table 1). The cumulative odds ratio for all studies was 0.51 (95% CI 0.47 to 0.56) (Figure 2).

DISCUSSION

This meta-analysis evaluates the impact of protocolized goal-directed hemodynamic optimization on short-term mortality in patients with severe sepsis and septic shock when initiated in the ED. Pooled data from the 25 included studies contain 9,597 subjects and demonstrate a 15.8% overall reduction in mortality. Our results underscore the importance of creating ED systems capable of identifying patients and delivering this care at the time of disease recognition.

A mounting body of evidence highlights the unacceptably high mortality rate among patients with severe sepsis and septic shock and suggests that an early quantitative resuscitation strategy can have a substantial survival benefit. Rivers et al first demonstrated the significant reduction in multi-organ dysfunction and mortality from septic shock that may be achieved with an ED-based protocol emphasizing early recognition and goal-directed therapy.[13] The Surviving Sepsis campaign, led by an international collaboration of critical care groups, endorsed the implementation of such a management strategy within the first 6 hours following recognition of septic shock and severe sepsis but did not mandate the involvement of the ED.[45]

Significant challenges confront the specialty of emergency medicine as it attempts to translate these research interventions and consensus guidelines to the bedside in the ED.[46] Indeed, some have suggested that EGDT trials are, in essence, a sepsis quality initiative challenging the existing paradigm of management, moving beyond the science and components of early hemodynamic optimization.[25] A pervasive question when considering how to deliver care based on the EGDT model in the ED is not simply whether the impact on outcomes is replicable but whether implementation of the protocol itself is. Of note, several of the trials identified in this systematic review appear to have been quality improvement initiatives in the ED based upon existing recommendations, with 2 of the trials performed in community hospital EDs.[26,31] However, when considering "feasibility" of translation to the bedside it is important to note we could only quantitatively extract the overall proportion of eligible patients receiving protocolized hemodynamic optimization from the following studies: Sebat et al[26] in their community hospital reported 100% sensitivity, Shapiro et al[22] missed 10 out of 138 eligible patients thus providing treatment to 92.7% of eligible patients, Patel et al in their community hospital reported that 19 of 78 patients didn't received bundled care in their hospital, thus providing treatment to 75.6% of eligible patients[31], and Sivayoham et al[33]—albeit in a retrospective cross-sectional study—reported that only 55.7% of eligible ED patients received EGDT.[33] Of note, results from the 2 community hospitals appear promising for the translation of protocols in that environment.

Perhaps influential on the results from the cumulative trials, there appears to be an increased awareness regarding severe sepsis and septic shock in the specialty of EM. Of note,

Table 3. Methodologic scores of identified trials that analyzed adult controlled trials implementing protocolized hemodynamic optimization in the emergency department for patients with severe sepsis and septic shock.

Author	Design	LOE Score
Rivers, 2001	Randomized control trial	1
Gao, 2005	Prospective observational study	3
Gaieski, 2005	Published abstract	5
Armstrong, 2005	Published abstract	5
Trzeciak, 2006	Prospective observational study with historical control	4
Shapiro, 2006	Prospective observational study with historical control	4
Ikeda, 2006	Published abstract	5
Kinsella, 2006	Published abstract	5
Mullon, 2006	Published abstract	5
Stenstrom, 2006	Published abstract	5
Antro, 2006	Published abstract	5
Micek, 2006	Prospective before and after study	3
Jones, 2007	Prospective before and after study	3
Nguyen, 2007	Prospective observational study	3
Sebat, 2007	Prospective observational study	3
Tanios, 2007	Published abstract	5
El Sohl, 2008	Prospective observational study with historical controls	4
Cannon, 2008	Published abstract	5
Gunaga, 2008	Published abstract	5
Puskarich, 2009	Prospective before and after study	3
Crowe, 2009	Prospective observational study with historical control	4
MacRedmond, 2010	Prospective observational study with historical control	4
Patel, 2010	Prospective observational study with historical control	4
Coba, 2011	Prospective observational study	3
Sivayoham, 2011	Retrospective before and after observational study	4

LOE, level of evidence

over the past decade the number of sepsis-related published abstracts have increased at EM national congresses with a 10-fold increase since the publication of the seminal EGDT trial in 2001 (Figure 3). Likewise, many of the identified small studies have attempted to replicate the Rivers study or implement the Surviving Sepsis Campaign guidelines and describe the impact of protocolizing hemodynamic optimization in the ED for patients with severe sepsis and septic shock. Our study systematically reviews this published body of literature in an effort to determine the overall impact of protocolized management when initiated *in the ED* on outcomes in severe sepsis and septic shock. In reporting the successful implementation of a sepsis protocol in the cited institutions, this meta-analysis offers the most compelling evidence to date that the EGDT model in the ED setting is potentially feasible and may improve patient outcomes. Of note, 2 of the trials were performed in community hospitals, suggesting that translation to that environment is also possible and yielding of better outcomes. Our results suggest the importance of creating systems capable of delivering hemodynamic optimization at the time of disease recognition in the ED.

However, the heterogeneity of the studies included in this meta-analysis with respect to both subject identification and management strategies yield a number of limitations that present challenges for future research and implementation. In developing an ED-based protocol for sepsis management, the identification strategy must clearly define whom to target for the management protocol. Rivers et al included patients with infection, 2 or more SIRS criteria, and shock as defined by a lactate $>$ 4mmol/L or hypotension despite plasma of volume expansion of 20cc/kg. Among published studies it is not possible to determine if patients with severe sepsis (ie—organ failure without lactate elevation or vasopressor dependence) benefit from protocolized hemodynamic optimization in the ED, or whether the outcome improvement was imparted only to those with septic shock. The impact of protocolized hemodynamic optimization in sepsis is not marginalized, but the patient population that EM must target remains to be

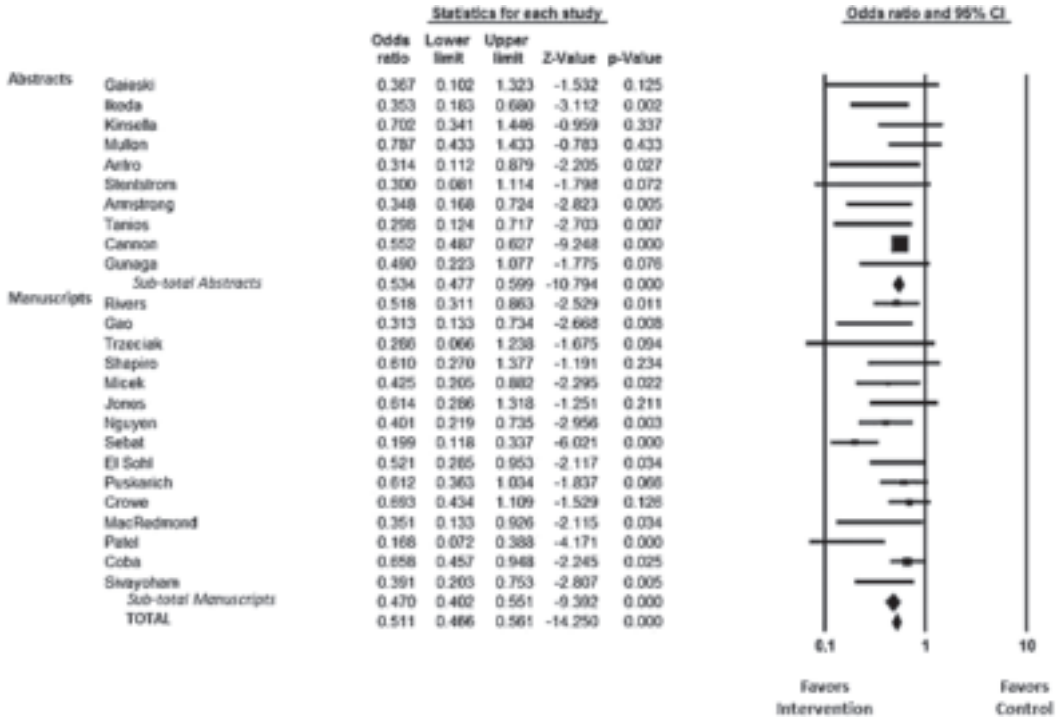

Figure 2. Relative risk of individual trials. Error bars indicate 95% confidence intervals. The pooled risk estimates are shown as diamonds.

defined with precision, as do the methods employed to reliably do so. Nevertheless, institution of early antibiotics as many of the protocols cited by identified studies have, is a critical intervention.

Likewise, a marked heterogeneity exists with respect to the elements of the protocolized care delivered in the studies included. All of the studies implemented a form of EGDT, but many included additional interventions such as low tidal volume ventilation, glycemic control, steroid administration, pulmonary artery catheter derived variables and/or the use of drotrcogin alfa outside the timeframe of the ED. It is not possible in these studies to discern which of the protocolized elements conferred the greatest mortality benefit and, as such, must be incorporated in an effective ED-based protocol initiative. Nor is it possible, in the case of studies with historical controls, to determine whether the mortality benefit was solely due to enhanced identification of patients with severe sepsis or shock. Nonetheless, many studies cite they were implementing other interventions consistent with the existing standard of care—which in many cases were also given to the control groups. Also, given that every identified study had an improvement in outcomes, the implementation of ED protocolized hemodynamic optimization appears to have an impact on mortality reduction for patients with severe sepsis and septic shock.

LIMITATIONS

This meta-analysis is limited by publication bias. However, to mitigate this potentially confounding variable we performed a systematic review of published abstracts at select national critical care and EM conferences. Nevertheless, if a study was not accepted as an abstract at a national conference, we did not have a mechanism for identification. Also, 4 of the studies enrolled patients from the floors or ICUs in addition to the ED, with only 2 of the 4 articles quantitatively reporting or estimating the number/proportion of patients enrolled from the ED without giving the exact number—Patel et al[31] stated in general terms that 80% of their patients are identified in the ED, with 20% being identified upon ICU admission. Gao et al[20]

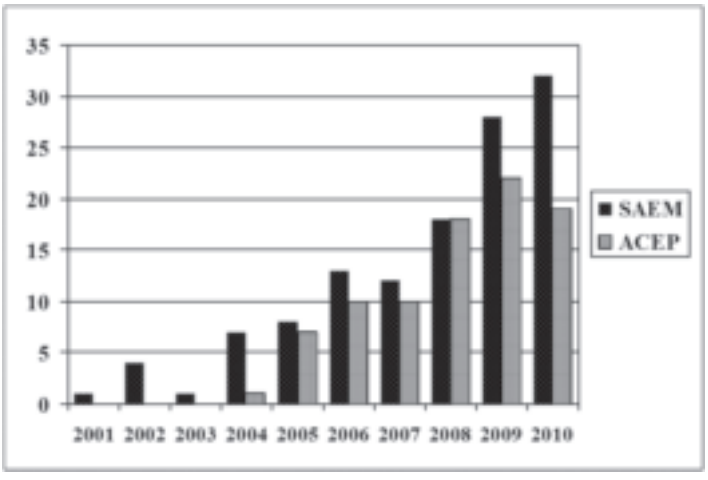

Figure 3. Number of sepsis abstracts at SAEM and ACEP national conferences since 2001. *SAEM*, Society for Academic Emergency Medicine Annual Meeting; *ACEP*, American College of Emergency Physicians Research Forum.

only had 11% enrolled from the ED. We have cited in the manuscript which studies only enrolled from the ED contrasted to others permitting ICU or medical/surgical floor enrollment. Interestingly, in the Coba et al article ED patients had greater compliance with interventions contrasted to the ICU environment.[32] We feel there is some merit to including these "hybrid" studies in our analysis—because many hospitals implementing sepsis protocols do so simultaneously in the ED, floors, and ICUs. Also, another limitation of this systematic review is that only one study was a randomized control trial with the others being either a before-after design, having a historical or retrospective control group, or having a cross-sectional design. Thus, many of these trials were subject to selection bias, length bias, completeness of data collection, and variability in practice patterns.

CONCLUSION

Implementation of protocolized hemodynamic optimization in the ED for patients with severe sepsis and septic shock appears to reduce mortality. The development of ED protocols to identify patients with severe sepsis and septic shock and achieve resuscitative endpoints merits strong consideration given the results from this meta-analysis. However, further confirmatory randomized control trials are necessary to determine which treatment components of a protocolized pathway are most beneficial and which specific patient population warrants these interventions in the ED setting.

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