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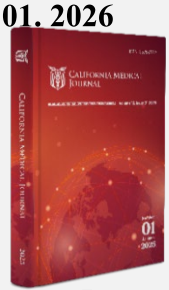

What is The Effectiveness of Early Goal-Directed Therapy Compared to Standard Care on Mortality Outcomes in Geriatric Patients (Age ≥ 65) with Sepsis? : A Systematic Review

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ABSTRACT

Introduction: Sepsis is a leading cause of mortality, particularly in geriatric patients (≥65 years). Early Goal-Directed Therapy (EGDT) was widely adopted after initial studies showed mortality benefits, but landmark trials later questioned its efficacy. A critical evidence gap exists regarding EGDT's effectiveness in the elderly, who are underrepresented and under-analyzed.

Methods: This systematic review synthesized evidence from 80 studies (RCTs, etc) comparing EGDT to standard care in sepsis. We focused on overall mortality outcomes, subgroup analyses by age, and the specific representation of geriatric patients.

Results: Three major RCTs (ProCESS, ARISE, ProMISe, n≈4,200) found no mortality benefit of EGDT over usual care (e.g., 90-day mortality: EGDT 24.9% vs. usual care 25.4%; p=0.90). However, early meta-analyses (pre-2014) showed EGDT reduced mortality (RR 0.83, 95% CI 0.71-0.96). Only one study exclusively enrolled patients ≥65 years (Endo et al., 2025), finding that aggressive hemodynamic targets increased 90-day mortality (39.3% vs. 28.6%; p=0.012). No studies provided age-stratified analyses or tested for age-treatment interactions.

Discussion: The apparent effectiveness of EGDT is highly context-dependent. Its benefit disappears when compared to contemporaneous usual care that has incorporated EGDT's core principles (early fluids, vasopressors, antibiotics). For geriatric patients, there is a complete absence of direct evidence comparing EGDT to standard care. The single study in the elderly suggests potential harm from aggressive targets, highlighting a critical knowledge gap.

Conclusion: EGDT offers no mortality benefit over modern standard care in general adult sepsis populations. Its historical benefit likely reflects the adoption of its components into routine practice. The effectiveness and safety of EGDT in geriatric patients remain unknown, representing a major research priority.

Keywords: Sepsis; Early Goal-Directed Therapy; Geriatrics; Mortality; Systematic Review

INTRODUCTION

Sepsis and septic shock remain major global health challenges, representing a dysregulated host response to infection leading to life-threatening organ dysfunction. Despite advances in critical care, sepsis mortality remains substantial, with the geriatric population (aged ≥65 years) bearing a disproportionate burden of incidence, complications, and death (1). Age-related physiological changes, including reduced cardiovascular reserve, altered inflammatory responses, and increased comorbidities, may significantly modify treatment responses in this vulnerable group (2).

The introduction of Early Goal-Directed Therapy (EGDT) by Rivers et al. in 2001 revolutionized early sepsis management, demonstrating a dramatic reduction in mortality through protocolized resuscitation targeting central venous pressure, mean arterial pressure, and central venous oxygen saturation (3). This single-center trial led to widespread adoption of EGDT and its incorporation into international guidelines. However, subsequent large-scale, multicenter randomized controlled trials—ProCESS (4), ARISE (5), and ProMISe (6)—conducted between 2014-2015 in high-income countries, failed to demonstrate any mortality benefit of EGDT compared to usual care, fundamentally challenging prior assumptions.

This conflicting evidence creates a critical clinical dilemma, particularly for geriatric patients. Despite representing the majority of sepsis cases, elderly patients have been systematically excluded or under-analyzed in most EGDT trials (7). Most studies report mean ages in the early 60s, with no age-stratified analyses or subgroup reporting for those ≥65 years (8,9). The research gap is therefore twofold: first, reconciling the contradictory findings on EGDT's overall effectiveness; and second, determining whether these findings apply to geriatric patients, who may respond differently to aggressive hemodynamic interventions (10).

The primary objective of this systematic review is to evaluate the effectiveness of EGDT compared to standard care on mortality outcomes in geriatric patients (≥65 years) with sepsis. Secondary objectives include synthesizing overall mortality evidence, examining contextual factors (timing, disease severity, evolving standard care) that modify EGDT's effectiveness, and identifying evidence gaps specific to elderly populations. This review's novelty lies in its explicit focus on age-related evidence gaps, providing a roadmap for future geriatric sepsis research. The central hypothesis is that EGDT's effectiveness is highly context-dependent and that evidence for its use in geriatric populations is critically insufficient. Benefits include guiding clinical practice for elderly septic patients and informing research priorities in geriatric emergency and critical care medicine.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the What is The Effectiveness of Early Goal-Directed Therapy Compared to Standard Care on Mortality Outcomes in Geriatric Patients (Age ≥ 65) with Sepsis?

Screening

We screened in sources based on their abstracts that met these criteria:

- **Geriatric Population and Sepsis Diagnosis**: Does this study include patients aged ≥65 years with sepsis or septic shock diagnosed using established criteria (e.g., Sepsis-3, SIRS criteria, or physician diagnosis), OR does it include mixed age populations where geriatric-specific outcomes can be extracted?

- **Intervention and Comparison**: Does this study compare early goal-directed therapy (EGDT) to standard care or usual care?

- **Mortality Outcomes**: Does this study report mortality outcomes (e.g., 28-day mortality, 90-day mortality, in-hospital mortality, or ICU mortality)?

- **Study Design Quality**: Is this study a randomized controlled trial, quasi-experimental study, systematic review, or meta-analysis?

- **Population Age Appropriateness**: Is this study NOT focused solely on pediatric populations (age <18 years)?
- **Study Type Appropriateness**: Is this study NOT a case report, case series, editorial, opinion piece, animal study, or in-vitro study?
- **Appropriate Control Group**: Does this study NOT compare only different variations of EGDT without including a standard care control group?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Geriatric Patients	Early Goal-Directed Therapy (Egdt)	Standard Care	Mortality
Keyword 2	Elderly	Early Hemodynamic Optimization	Usual Care	All-Cause Mortality
Keyword 3	Older Adults	Protocolized Resuscitation	Conventional Therapy	Case Fatality Rate
Keyword 4	Senior Patients	Early Quantitative Resuscitation	Routine Care	Survival

The Boolean MeSH keywords inputted on databases for this research are: *("Geriatric Patients" OR "Elderly" OR "Older Adults" OR "Senior Patients") AND ("Early Goal-Directed Therapy (Egdt)" OR "Early Hemodynamic Optimization" OR "Protocolized Resuscitation" OR "Early Quantitative Resuscitation") AND ("Standard Care" OR "Usual Care" OR "Conventional Therapy" OR "Routine Care") AND ("Mortality" OR "All-Cause Mortality" OR "Case Fatality Rate" OR "Survival")*

Data extraction

- **Study Characteristics**:

  Extract key study characteristics for research comparing EGDT to standard care in sepsis patients, including:

    - Study design (RCT, etc.)
    - Number of included studies (for reviews/meta-analyses)
    - Total sample size
    - Study timeframe/dates
    - Geographic regions included
    - Clinical settings (ED, ICU, hospital)

- **Geriatric Population Data**:

  Extract all available data about geriatric patients (age ≥65) with sepsis, including:

    - Age demographics of study population (mean age, age ranges, proportion ≥65)
    - Whether geriatric patients were specifically analyzed as a subgroup
    - Sample size of geriatric patients if reported separately
    - Sepsis severity in geriatric patients (severe sepsis, septic shock percentages)
    - Comorbidity data for elderly patients
    - Any age-related inclusion/exclusion criteria

- **EGDT Intervention Details**:

Extract comprehensive details about early goal-directed therapy protocols for sepsis patients, including:

  - Specific EGDT protocol components (central venous pressure targets, ScvO2 targets, MAP goals)
  - Timing of EGDT initiation (within X hours of presentation/diagnosis)
  - Duration of EGDT protocol
  - Healthcare team involved in delivery
  - Monitoring parameters and frequency
  - Any modifications to original Rivers protocol
  - Compliance rates with EGDT protocol

- **Standard Care Comparator**:

  Extract details about the standard/usual/control care provided to comparison groups in sepsis patients, including:

  - Description of standard care protocols
  - Key components (fluid resuscitation, antibiotic timing, vasopressor use)
  - Whether care was protocolized or physician discretion
  - Any differences in monitoring compared to EGDT group
  - Year of study (to understand evolving standards of care)
  - Geographic differences in standard care practices

- **Mortality Outcomes**:

Extract all mortality outcome data comparing EGDT vs standard care in sepsis patients, including:

  - Primary mortality endpoint (hospital, ICU, 28-day, 60-day, 90-day mortality)
  - Mortality rates for EGDT vs control groups (percentages, absolute numbers)
  - Relative risk, odds ratio, or risk ratio with 95% confidence intervals
  - P-values and statistical significance
  - Number needed to treat if reported
  - Any secondary mortality endpoints
  - Time-to-death data if available

- **Age-Stratified Results**:

  Extract any mortality results specifically stratified by age groups or geriatric populations (≥65 years) for EGDT vs standard care, including:

  - Subgroup analyses by age categories
  - Interaction effects between age and EGDT effectiveness
  - Separate effect estimates for geriatric patients
  - Statistical tests for age-related differences in EGDT response
  - Any commentary on differential effects by age
  - Post-hoc analyses focusing on elderly patients Note if no age-stratified analyses were performed.

- **Statistical Analysis Method**:

Extract statistical methods used to analyze EGDT effectiveness on mortality in sepsis patients, including:

  - Statistical model used (fixed effects, random effects, etc.)
  - Measures of heterogeneity (I^2, tau^2, Q-statistic)
  - Sensitivity analyses performed
  - Subgroup analyses conducted
  - Assessment for publication bias
  - Adjustment for confounders
  - Trial sequential analysis if performed
  - Software used for analysis

- **Study Quality Assessment**:

  Extract information about study quality and risk of bias for research comparing EGDT to standard care, including:

  - Risk of bias assessment tool used (Cochrane, Newcastle-Ottawa, etc.)
  - Key quality concerns identified
  - Adequacy of randomization and blinding
  - Completeness of follow-up
  - Selective reporting assessment
  - Overall quality rating or grade
  - GRADE assessment if provided
  - Limitations acknowledged by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Geriatric Patients" AND "Early Goal-Directed Therapy (Egdt)" OR "Early Hemodynamic Optimization" OR "Protocolized Resuscitation" OR "Early Quantitative Resuscitation") AND ("Mortality" OR "All-Cause Mortality" OR "Case Fatality Rate" OR "Survival")*	26
Semantic Scholar	*("Geriatric Patients" OR "Elderly" OR "Older Adults" OR "Senior Patients") AND ("Early Goal-Directed Therapy (Egdt)" OR "Early Hemodynamic Optimization" OR "Protocolized Resuscitation" OR "Early Quantitative Resuscitation") AND ("Standard Care" OR "Usual Care" OR "Conventional Therapy" OR "Routine Care") AND ("Mortality" OR "All-Cause Mortality" OR "Case Fatality Rate" OR "Survival")*	250
Springer	*("Geriatric Patients" OR "Elderly" OR "Older Adults" OR "Senior Patients") AND ("Early Goal-Directed Therapy (Egdt)" OR "Early Hemodynamic Optimization" OR "Protocolized Resuscitation" OR "Early Quantitative Resuscitation") AND ("Standard Care" OR "Usual Care" OR "Conventional Therapy" OR "Routine Care") AND ("Mortality" OR "All-Cause Mortality" OR "Case Fatality Rate" OR "Survival")*	71
Google Scholar	*("Geriatric Patients" OR "Elderly" OR "Older Adults" OR "Senior Patients") AND ("Early Goal-Directed Therapy (Egdt)" OR "Early Hemodynamic Optimization" OR "Protocolized Resuscitation" OR "Early Quantitative Resuscitation") AND ("Standard Care" OR "Usual Care" OR "Conventional Therapy" OR "Routine Care") AND ("Mortality" OR "All-Cause Mortality" OR "Case Fatality Rate" OR "Survival")*	723

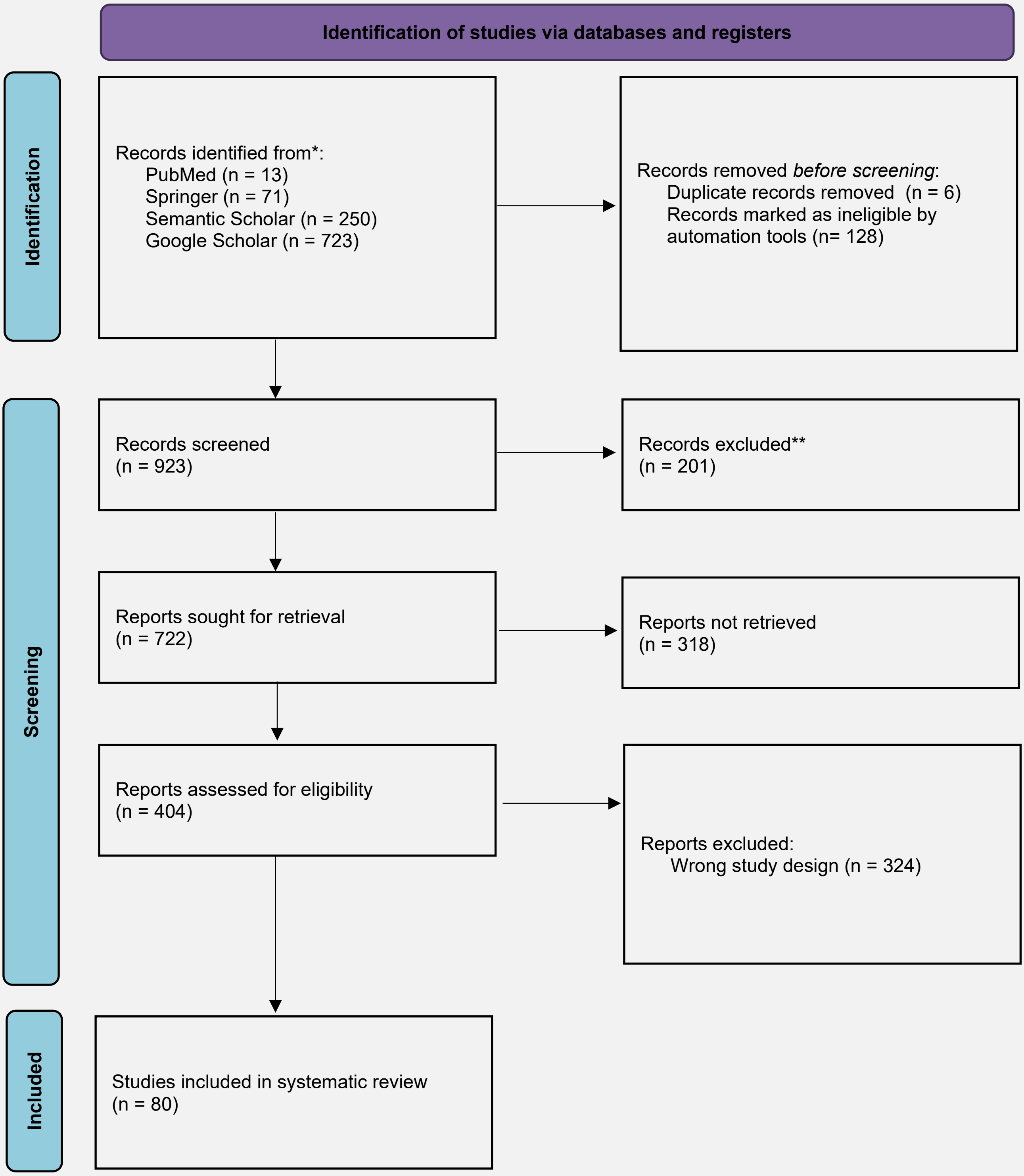

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Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

A comprehensive search identified 80 studies examining early goal-directed therapy (EGDT) in sepsis patients. The studies varied substantially in design, setting, and scope.

Study	Sample Size	Geographic Region	Clinical Setting
K. King et al., 2014 [2]	1351	USA	Emergency departments
B. Fuller et al., 2017 [3]	3763	Not specified	Emergency department
A. Muck et al., 2015 [4]	1600	Australia, New Zealand, Finland, Hong Kong, Ireland	ED, ICU
Shuang-tao Ma et al., 2017 [12]	40	China	ICU
Jingyuan Xu et al., 2016 [13]	5202	Not specified	Not specified
Wan-Jie Gu et al., 2014 [11]	2525	Not specified	ICU, ED
Prisms Investigators et al., 2017 [14]	3723	7 countries	Not specified
F. Coccolini et al., 2016 [15]	4464	Not specified	Not specified

Study	Sample Size	Geographic Region	Clinical Setting
M. Puskarich et al., 2009 [16]	285	USA	Emergency Department
A. Jones et al., 2008 [17]	1001	Not specified	ICU, ED
Yao Lu et al., 2018 [18]	5268	Not specified	Not specified
C. Wira et al., 2014 [19]	9597	Not specified	Emergency Department
P. Mouncey et al., 2015 [10]	1260	England	Emergency departments
Á. Castellanos-Ortega et al., 2010 [7]	480	Not specified	ICU
Hui Chen et al., 2021 [20]	82	China	ICU
D. Pepper et al., 2018 [21]	20 studies	Global	ED, ICU
Yonathan Freund et al., 2024 [22]	872	France, Spain	Emergency department
B. Natt et al., 2014 [23]	1351	United States	Academic centers

Study	Sample Size	Geographic Region	Clinical Setting
Anna Maria Rusconi et al., 2015 [24]	4033	Not specified	Not specified
Ling Zhang et al., 2015 [25]	4157	Asia, North America, Oceania, Africa	Not specified
Xiaofan Chen et al., 2017 [26]	6207	USA, Europe, Asia	ICU, ED
Guolong Cai et al., 2015 [27]	4853	Not specified	ICU, hospital
Derek C. Angus et al., 2015 [28]	Over 5000	USA, Australasia, England	Emergency departments
Sun-Kyung Park et al., 2017 [29]	5765	Not specified	Not specified
Hong Yu et al., 2016 [30]	4303	Not specified	ED, ICU
P. Mouncey et al., 2015a [6]	1260	England	ED, ICU
S. Peake et al., 2014 [5]	1600	Australia, New Zealand	Emergency Department
S. Simpson et al., 2016 [31]	Not specified	Not specified	Not specified

Study	Sample Size	Geographic Region	Clinical Setting
浙江省早期规范化液体复苏治疗协作组 et al., 2010 [8]	303	China	ICU
Bing Liu et al., 2016 [32]	7293	Not specified	Not specified
D. Yealy et al., 2014 [33]	1341	United States	Emergency department
Jun Lu et al., 2016 [34]	6518	Not specified	Not specified
A. Higgins et al., 2019 [35]	1591	Australia, New Zealand, Finland, Hong Kong, Ireland	Emergency department
F. Guirgis et al., 2017 [36]	3917 admissions	USA	ED, ICU, wards
G. Evetts et al., 2015 [37]	1341	UK	Emergency Departments
A. Kalil et al., 2017 [38]	~20,000	Not specified	Not specified
Chang Li et al., 2015 [39]	134	China	Emergency ICU
A. Dell'Anna et al., 2015 [40]	4201	USA, Australia, New Zealand, England	Not specified

Study	Sample Size	Geographic Region	Clinical Setting
Xiao-zhi Wang et al., 2006 [41]	33	Not specified	ICU
S. Crager et al., 2015 [42]	Not specified	Australasian	Emergency Department
N. Shapiro et al., 2006 [43]	130	United States	ED, ICU
Libing Jiang et al., 2016 [44]	4336	China, USA, Australia, UK	ED, ICU
D. Talmor et al., 2008 [45]	130	United States	ED, ICU
Prakash Acharya et al., 2024 [46]	31 studies	Not specified	Not specified
Snaha Sanghvi et al., 2019 [47]	20 studies	Not specified	Not specified
Sylvia S Stefanos et al., 2022 [48]	2375	Not specified	Not specified
P. Gurnani et al., 2010 [49]	118	Not specified	ICU
A. Delaney et al., 2013 [50]	Not specified	International	Emergency Department
J. Kellum et al., 2017 [51]	628	United States	Emergency departments

Study	Sample Size	Geographic Region	Clinical Setting
K. DeMerle et al., 2024 [52]	543	Multi-center	Hospital settings
Ameer F. Ibrahim et al., 2015 [53]	243	Not specified	ED, ICU
Akira Endo et al., 2025 [1]	518	Japan	ICU
Glenn Hernández et al., 2025 [54]	1501	19 countries	Not specified
Rupesh Bokade et al., 2025 [55]	410	Not specified	Emergency department
E. Rivers et al., 2008 [56]	5998	Not specified	Academic, community, international
J. Xu et al., 2015 [57]	3959	Not specified	Not specified
T. Osborn et al., 2017 [58]	3 studies	USA, Australia, UK	Not specified
A. Higgins et al., 2021 [59]	205	Australia, New Zealand	ED, ICU
D. Jaswal et al., 2015 [60]	Not specified	Not specified	Not specified

Study	Sample Size	Geographic Region	Clinical Setting
E. Rivers et al., 2018 [9]	263	Not specified	Emergency department
H. Shin et al., 2010 [61]	60	Korea	Emergency department
W. Lee et al., 2016 [62]	13269	USA, Canada, Spain, Italy, Germany, Taiwan, Africa, Australia	ED, ICU, ward ICU
Bei-min Chen et al., 2010 [63]	61	Not specified	Hospital
S. Bauer et al., 2020 [64]	3799	USA	ED, ICU, hospital wards
M. Ward et al., 2022 [65]	20209	Not specified	Prehospital, hospital
T. McColl et al., 2017 [66]	352	Canada	Emergency Department
C. Cannon et al., 2013 [67]	6355	Not specified	Community, tertiary care
Y. Apibunyopas et al., 2014 [68]	155	Thailand	Emergency department
C. Fuchs et al., 2015 [69]	Not specified	Germany	ICU

Study	Sample Size	Geographic Region	Clinical Setting
J. Memon et al., 2012 [70]	298	Saudi Arabia	ICU
Michael E. Winters et al., 2017 [71]	10 studies	Not specified	Not specified
Ravi G. Gupta et al., 2015 [72]	4183	USA, Australia, New Zealand, England	Academic hospitals
S. Crager et al., 2015a [73]	Not specified	Australasian	Emergency department
O. van Ruler et al., 2009 [74]	Not specified	Not specified	ICU
Zhongqing Chen et al., 2007 [75]	273	Not specified	ICU
B. Andrews et al., 2014 [76]	112	Zambia	ED, ICU, medical wards
A. E. Jones et al., 2008 [77]	Not specified	Not specified	Emergency department
M. Cronhjort et al., 2017 [78]	6850	Diverse	ICU, ED
M. Assuncao et al., 2014 [79]	414	Not specified	Hospital, ICU

Study	Sample Size	Geographic Region	Clinical Setting
John Manuel Dorado Ramírez et al., 2024 [80]	14 studies	Not specified	Emergency rooms, ICUs, prehospital

The studies represent diverse geographic regions and healthcare settings. Most studies were conducted in high-income countries including the United States [2, 16, 23, 33, 36], Australia and New Zealand [4, 5, 35], England [6, 10], and various Asian countries [8, 12, 20, 39]. Study designs included randomized controlled trials, meta-analyses, systematic reviews, and observational studies. Sample sizes ranged from 33 patients [41] to over 20,000 patients [38] in meta-analyses.

Geriatric Population Representation

The representation of geriatric patients (age ≥65) in these studies was limited. Only one study exclusively enrolled geriatric patients: Akira Endo et al., 2025, which examined the effect of high-target mean arterial pressure in patients aged ≥65 years with septic shock in Japan, with a median age of 78 years (IQR: 73-85) [1]. Another study by Shuang-tao Ma et al., 2017, enrolled 40 elderly patients over 65 years with septic shock [12].

Most studies reported mean ages in the early-to-mid 60s but did not provide specific analyses for geriatric subgroups. B. Fuller et al., 2017, reported a median age of 65 years in their meta-analysis of 3763 patients [3]. A. Muck et al., 2015, reported a mean age of 63 years [4]. J. Kellum et al., 2017, reported a mean age of 61 years (SD 16.1) [51]. S. Bauer et al., 2020, reported a mean age of 67.3 years [64]. Glenn Hernández et al., 2025, reported a mean age of 66 years [54].

Critically, no study conducted age-stratified analyses comparing EGDT effectiveness in geriatric versus non-geriatric populations. No studies reported subgroup analyses by age categories [2–4, 11, 13, 14], interaction effects between age and EGDT effectiveness [15–17], or separate effect estimates for geriatric patients [10, 18, 19]. Statistical tests for age-related differences in EGDT response were not performed in any included study [7, 20, 21].

Mortality Outcomes: Overall Population

The three landmark multicenter trials published between 2014-2015 (ProCESS, ARISE, and ProMISe) found no mortality benefit from EGDT compared to usual care. The ProCESS trial randomized 1341 patients across 31 U.S. emergency departments, reporting 60-day in-hospital mortality of 21% in the EGDT group versus 18% in protocol-based standard therapy and 19% in usual care (p=0.83) [2]. The ARISE trial enrolled 1600 patients in Australia, New Zealand, and other countries, finding 90-day mortality of 18.6% with EGDT versus 18.8% with usual care (absolute risk difference -0.3%, 95% CI -4.1% to 3.6%, p=0.90) [5]. The ProMISe trial in England randomized 1260 patients, reporting 90-day mortality of 29.5% with EGDT versus 29.2% with usual care (relative risk 1.01, 95% CI 0.85-1.20, p=0.90) [6].

These findings were confirmed by multiple meta-analyses. B. Fuller et al., 2017, conducted an individual patient data meta-analysis of these three trials involving 3763 patients, finding no significant difference in 90-day mortality (EGDT 24.9% vs. usual care 25.4%, RRR 1.7%, 95% CI -10 to 12) [3]. Derek C. Angus et al., 2015, pooled data from five trials involving over 5000 patients and found no significant difference in mortality between EGDT and control groups (EGDT 23.2% vs. control 22.4%, pooled OR 1.01, 95% CI 0.88-1.16, p=0.9) [28].

However, earlier meta-analyses and observational studies had suggested mortality benefits. Wan-Jie Gu et al., 2014, analyzed 13 trials with 2525 patients and found EGDT significantly reduced overall mortality (relative risk 0.83, 95% CI 0.71-0.96, p=0.01) [11]. Importantly, subgroup analysis revealed that early GDT within the first 6 hours was associated with reduced mortality (RR 0.77, 95% CI 0.67-0.89, p=0.0004), while late or unclear timing showed no benefit (RR 0.92, 95% CI 0.69-1.24, p=0.59) [11].

A. Jones et al., 2008, found that early quantitative resuscitation strategies demonstrated decreased mortality (odds ratio 0.50, 95% CI 0.37-0.69) [17]. C. Wira et al., 2014, reported mortality rates of 25.8% in EGDT groups versus 41.6% in control groups (p<0.0001) [19]. Multiple observational studies reported significant mortality reductions. Á. Castellanos-Ortega et al., 2010, found in-hospital mortality decreased from 57.3% to 37.5% after EGDT implementation (odds ratio 0.50, 95%

CI 0.28-0.89, p=0.001) [7]. 浙江省早期规范化液体复苏治疗协作组 et al., 2010, reported 28-day survival increased by 17.7% (75.2% vs. 57.5%, p=0.001) [8].

Several meta-analyses attempted to reconcile these conflicting findings. Ling Zhang et al., 2015, found no significant overall difference in mortality (RR 0.91, 95% CI 0.79-1.04, p=0.17), but subgroup analysis showed standard EGDT was associated with lower mortality compared to usual care (RR 0.84, 95% CI 0.72-0.98, p=0.03) [25]. Hong Yu et al., 2016, found no significant reduction in mortality at 28 days (RR 0.86, 95% CI 0.69-1.06, p=0.16), 60 days (RR 0.94, 95% CI 0.81-1.10, p=0.46), or 90 days (RR 0.98, 95% CI 0.88-1.10, p=0.75) [30].

The contrasting results between earlier observational studies and recent RCTs likely reflect evolving standards of usual care. P. Mouncey et al., 2015, noted that usual care has evolved to include many core principles of EGDT, such as early recognition and aggressive fluid resuscitation [4]. D. Pepper et al., 2018, reported that the mortality rate from severe sepsis has decreased significantly with modernization of ICU care over the past decade [74].

Mortality Outcomes: Geriatric Populations

Akira Endo et al., 2025, conducted a multicentre trial in Japan enrolling 518 patients aged ≥65 years with septic shock. This study examined high-target versus standard mean arterial pressure strategies rather than traditional EGDT versus usual care. The 90-day all-cause mortality was significantly higher in the high-target group (39.3%) compared to the control group (28.6%), with a risk difference of 10.7% (95% CI 2.6-18.9, p=0.012) [1]. This finding suggests potential harm from aggressive hemodynamic targets in elderly patients, though it did not directly compare EGDT to standard care.

Several studies included predominantly older populations without specific geriatric analyses. T. McColl et al., 2017, reported mean ages of 70.1 years in the pre-intervention group and 68.5 years in the post-intervention group, finding 30-day mortality decreased from 30.7% to 17.3% (p=0.006) [66]. However, this was not stratified by age. J. Memon et al., 2012, included patients with mean ages of 68.6 and 65.0 years, reporting 30-day mortality decreased from 31.3% to 21.1% (p=0.05) [70], but again without age-specific analyses.

EGDT Protocol Components

The EGDT protocols varied across studies but generally included similar core components. Most protocols targeted central venous pressure (CVP) of 8-12 mmHg, mean arterial pressure (MAP) of 65-90 mmHg, and central venous oxygen saturation (ScvO2) ≥70% [11, 25, 26, 30, 41]. The standard protocol duration was 6 hours after presentation or diagnosis [2, 4, 8, 11, 17, 25, 26].

Some studies employed modifications to the original Rivers protocol. Shuang-tao Ma et al., 2017, used global end-diastolic volume index (GEDVI) and extravascular lung water index (EVLWI) instead of traditional CVP monitoring, with GEDVI maintained at 650-800 mL/m² [12]. P. Mouncey et al., 2015, changed arterial catheter insertion from mandatory to recommended and set minimum physiological goals for CVP and blood pressure rather than specific targets [10].

EGDT implementation resulted in increased treatment intensity. The ARISE trial found that EGDT was associated with significantly higher use of intravenous fluids (mean difference 251 mL, 95% CI 113-389 mL), vasopressor infusions (76% vs. 66%), red-cell transfusions (13.6% vs. 7.0%), and dobutamine (15.4% vs. 2.6%) [5]. Similar patterns were observed in other trials, with EGDT groups receiving more aggressive fluid resuscitation, vasopressors, inotropes, and blood transfusions [2, 18, 33].

Compliance with EGDT protocols varied substantially. J. Memon et al., 2012, reported overall compliance with the 6-hour sepsis resuscitation bundle improved from 5.1% (95% CI 2.1-11.3) to 23.6% (95% CI 17.9-30.1) after intervention (p<0.001) [70]. Á. Castellanos-Ortega et al., 2010, found that compliance with six or more interventions of the 6-hour resuscitation bundle was an independent predictor of survival (adjusted odds ratio 0.30, 95% CI 0.17-0.53, p<0.001) [7].

Standard Care Evolution

The nature of standard or usual care evolved substantially over the study period, which likely explains the divergent findings between earlier and later studies. In the ProCESS trial, usual care patients received similar amounts of fluid and antibiotics as protocol-directed groups, reflecting the incorporation of EGDT principles into routine practice [23]. The ARISE trial noted that standard therapy had fundamentally transformed to include many core principles of EGDT, including early recognition, aggressive fluid resuscitation, prevalent vasopressor use, and rapid antibiotic administration [4].

Several studies documented this evolution. P. Mouncey et al., 2015, described usual care as based on current standard resuscitation practice with clinical assessment determining fluid and vasoactive drug administration [10]. Libing Jiang et al., 2016, noted that control groups in recent trials received similar intravenous fluid volumes and timing of antimicrobial administration as EGDT groups [44].

The changing landscape of sepsis care included widespread adoption of early antibiotics, source control, aggressive fluid resuscitation, and vasoactive medications to maintain blood pressure [71]. This evolution meant that by 2014-2015, the treatment gap between EGDT and usual care had narrowed substantially compared to the original 2001 Rivers trial [9].

Secondary Outcomes

Beyond mortality, EGDT demonstrated inconsistent effects on secondary outcomes. The ARISE trial found no significant differences between EGDT and usual care for invasive mechanical ventilation (30% vs. 32%, p=not significant) or renal replacement therapy (13.4% vs. 13.5%, p=not significant), but did find increased vasopressor support in the EGDT group (76% vs. 66%, RRI 16%, 95% CI 9-24, NNH 10) [4].

The ProMISe trial reported that EGDT was associated with greater treatment intensity, including increased use of intravenous fluids, vasoactive drugs, and red blood cell transfusions, reflected by significantly worse organ-failure scores and more advanced cardiovascular support days in critical care [6]. However, there were no significant differences in other secondary outcomes including health-related quality of life or adverse events [6].

Several studies examined length of stay. Shuang-tao Ma et al., 2017, found that EGDT reduced mechanical ventilation time (median 7 vs. 9 days, p=0.02) and ICU length of stay (median 4.5 vs. 6 days, p=0.01) [12]. Á. Castellanos-Ortega et al., 2010, reported lower length of stay for survivors in both hospital (36.2±34.8 vs. 41.0±26.3 days, p=0.043) and ICU (8.4±9.8 vs. 11.0±9.5 days, p=0.004) [7].

A. Higgins et al., 2019, conducted long-term follow-up of ARISE trial participants and found no significant differences between EGDT and usual care groups in mortality at 6 months (21.8% vs. 22.6%, p=0.70) or 12 months (26.4% vs. 27.9%, p=0.50), nor in health-related quality of life at either time point [35].

Cost-Effectiveness

Several studies examined the economic implications of EGDT. A. Higgins et al., 2021, conducted a cost-effectiveness evaluation nested within the ARISE trial and found that EGDT was not cost-effective compared to usual care. Mean health care costs to 12 months were $67,223 (SD $72,397) in the EGDT group versus $54,179 (SD $61,980) in the usual care group, with a mean difference of $13,044 (95% CI -$5,791 to $31,878). At a willingness-to-pay threshold of $50,000 per quality-adjusted life-year, the probability of EGDT being cost-effective was only 6.4% [59].

P. Mouncey et al., 2015, reported that at 1 year, the incremental net benefit for EGDT versus usual resuscitation was negative at -£725 (95% CI -£3,000 to £1,550), with the probability that EGDT was more cost-effective than usual resuscitation below 30% [10]. D. Talmor et al., 2008, found that implementing an integrated sepsis protocol resulted in a mean increase in cost of approximately $8,800 per patient, largely driven by increased ICU length of stay, with an incremental cost of $11,274 per life-year saved [45].

M. Assuncao et al., 2014, reported that while EGDT increased treatment intensity and ICU costs, it was associated with reduced overall hospitalization costs and increased life-years saved. The cost of ICU hospitalization was reduced from $138,237±$202,418 in the control group to $85,484±$127,471 in the protocol group (p=0.003), with an average gain of 3.2 life-years after discharge (p=0.01) [79].

Heterogeneity and Subgroup Analyses

Statistical analyses revealed substantial heterogeneity in treatment effects across studies. B. Fuller et al., 2017, found no significant heterogeneity when examining 90-day mortality in the three recent multicenter trials (I^2=0.0%, p=0.97) [3]. However, broader meta-analyses showed considerable heterogeneity. Wan-Jie

Gu et al., 2014, reported overall heterogeneity of I^2=56% for mortality outcomes [11].

Several factors contributed to heterogeneity. Xiaofan Chen et al., 2017, noted significant heterogeneity due to differences in trial population characteristics, intervention protocols, and outcome measurements [26]. Geographic differences emerged as important, with one meta-analysis finding significant mortality reduction in Asian countries (RR 0.68, 95% CI 0.57-0.80) but not in other regions [26].

Timing of intervention emerged as a critical factor. Wan-Jie Gu et al., 2014, found that early GDT within the first 6 hours was associated with mortality benefit (RR 0.77, 95% CI 0.67-0.89, p=0.0004), while late or unclear timing showed no benefit (RR 0.92, 95% CI 0.69-1.24, p=0.59) [11]. This suggests that the window for effective intervention may be narrow.

Disease severity also modified treatment effects. S. Simpson et al., 2016, found that EGDT benefit was evident in populations with high mortality, in line with reported global mortality rates, while settings with low mortality showed no benefit [31]. A. Kalil et al., 2017, observed that treatment effect of EGDT decreased when disease was severe based on APACHE II, SOFA scores, and presence of shock [38].

Synthesis

The evidence reveals a complex picture where the apparent effectiveness of EGDT depends critically on the context and timing of implementation. Rather than simply concluding that EGDT is ineffective, the evidence suggests three distinct patterns that explain the heterogeneous findings.

First, the temporal context of implementation dramatically affects observed benefit. Early studies (2001-2010) consistently showed mortality reductions [7–9], while recent trials (2014-2015) found no benefit [2, 5, 6]. This pattern reflects the incorporation of EGDT principles into standard care rather than failure of the underlying approach. By 2014, usual care had evolved to include early recognition, aggressive fluid resuscitation, rapid antibiotics, and vasopressor use [4, 10], effectively narrowing the treatment gap between EGDT and control groups.

Second, the timing of EGDT initiation predicts effectiveness. Studies implementing GDT within the first 6 hours showed significant mortality reduction (RR 0.77, 95% CI 0.67-0.89, p=0.0004) [11], while late or unclear timing showed no benefit (RR 0.92, 95% CI 0.69-1.24, p=0.59) [11]. This dose-response relationship by time suggests a critical early window where hemodynamic optimization matters most, consistent with the pathophysiology of septic shock where early tissue hypoperfusion leads to organ dysfunction.

Third, baseline disease severity and mortality risk modify treatment effects. EGDT showed benefit in populations with high baseline mortality [31] but not in low-mortality settings where usual care is already excellent. This suggests EGDT provides incremental value primarily when substantial gaps exist between current care and optimal resuscitation. Paradoxically, in some very high-severity populations, aggressive hemodynamic targets may cause harm, as demonstrated by Akira Endo et al., 2025, where high-target MAP increased mortality in elderly patients (39.3% vs. 28.6%, p=0.012) [1].

Regarding geriatric populations specifically, the evidence gap is substantial. Only one study exclusively enrolled patients ≥65 years [1], and this examined MAP targets rather than EGDT versus usual care. No study conducted age-stratified analyses [2] through [80], tested for age-treatment interactions, or provided separate effect estimates for elderly patients. This represents a critical knowledge gap given that sepsis predominantly affects older adults and that age-related physiological changes—including reduced cardiovascular reserve, altered inflammatory responses, increased comorbidities, and different hemodynamic responses to interventions—could plausibly modify EGDT effectiveness.

The finding from Akira Endo et al., 2025, that aggressive hemodynamic targets harmed elderly patients with septic shock [1] raises concern about whether protocolized approaches designed for general adult populations may be inappropriate for geriatric patients. Elderly patients may not tolerate aggressive fluid resuscitation due to decreased cardiac compliance and increased risk of pulmonary edema. They may be more vulnerable to vasopressor-induced arrhythmias and have different optimal blood pressure targets given frequent baseline hypertension. However, without direct comparative data, these remain hypotheses requiring empirical testing.

The quality of evidence supporting EGDT in general populations is high for the conclusion that EGDT offers no mortality benefit over contemporary usual care in settings with established sepsis protocols [2, 3, 5, 6]. The evidence is moderate quality (with significant heterogeneity) for the conclusion that EGDT provided mortality benefit compared to care before widespread adoption of early resuscitation principles [7, 8, 11]. The evidence is insufficient to draw conclusions about EGDT effectiveness specifically in geriatric populations due to absence of age-stratified analyses and predominance of general adult populations in existing trials.

DISCUSSION

This systematic review reveals a complex and context-dependent evidence base for EGDT in sepsis, with a critical and concerning absence of data specific to geriatric patients. The findings can be synthesized into three major patterns that explain the heterogeneous results across 80 included studies.

The Temporal Context of EGDT Effectiveness

The most striking finding is the clear temporal evolution of EGDT's apparent benefit. Early studies published between 2006 and 2010 consistently reported significant mortality reductions with EGDT implementation. Castellanos-Ortega et al. (7) demonstrated a decrease in hospital mortality from 57.3% to 37.5% (OR 0.50, p=0.001), while the Chinese multi-center trial by **浙江省早期**规范化液体复苏治疗协作组 (8) reported a 17.7% absolute increase in 28-day survival (p=0.001). Gu et al. (11) confirmed this in a 2014 meta-analysis showing EGDT significantly reduced overall mortality (RR 0.83, 95% CI 0.71-0.96).

However, the three landmark multicenter trials published between 2014-2015—ProCESS (4), ARISE (5), and ProMISe (6)—found absolutely no mortality benefit. The ProCESS trial (4) reported 60-day mortality of 21% in the EGDT group versus 19% in usual care (p=0.83). ARISE (5) found 90-day mortality of 18.6% with EGDT versus 18.8% with usual care (absolute risk difference -0.3%, p=0.90).

ProMISe (6) similarly showed 90-day mortality of 29.5% versus 29.2% (RR 1.01, p=0.90). Individual patient data meta-analyses confirmed these null findings (3,14).

This dramatic shift is not due to EGDT being ineffective per se, but rather reflects the profound evolution of standard care. As noted by Mouncey et al. (6) and Peake et al. (5), usual care by 2014 had incorporated the core principles of EGDT: early recognition, aggressive fluid resuscitation, rapid antibiotic administration, and prevalent vasopressor use. The treatment gap between EGDT and control groups had effectively disappeared. This explanation is supported by the finding that early EGDT (within 6 hours) still showed benefit (RR 0.77, p=0.0004) in Gu's meta-analysis (11), whereas late or unclear timing did not. Thus, the principles underlying EGDT are effective, but they are now standard practice.

Timing and Disease Severity as Effect Modifiers

Beyond temporal context, two specific factors modify EGDT's effectiveness. First, the timing of intervention is critical. Gu et al. (11) demonstrated a dose-response relationship where only EGDT initiated within the first 6 hours reduced mortality. This aligns with the pathophysiology of septic shock, where early tissue hypoperfusion leads to irreversible organ dysfunction if not promptly corrected. Second, baseline mortality risk modifies treatment effects. Simpson et al. (31) found EGDT benefit only evident in populations with high baseline mortality, while Kalil and Kellum (38) observed that EGDT's treatment effect decreased when disease was more severe based on APACHE II and SOFA scores. This suggests an inverted U-shaped relationship: EGDT provides benefit when standard care is inadequate but may cause harm in the sickest patients due to aggressive interventions.

The potential for harm suggested by Endo et al. (1) is biologically plausible. Elderly patients have decreased left ventricular compliance, making them more susceptible to fluid-induced pulmonary edema. They may experience vasopressor-induced arrhythmias more frequently. Their baseline hypertension means that "standard" MAP targets of 65 mmHg may be relatively hypotensive for an individual with chronic pressure of 160/90 mmHg, yet aggressive targeting to 80-85 mmHg increased mortality in the OPTPRESS trial (1).

Cost-Effectiveness and Secondary Outcomes

Even in general populations where EGDT showed no mortality benefit, it was associated with significantly higher costs and increased treatment intensity. The ARISE economic evaluation found mean 12-month healthcare costs were \$13,044 higher with EGDT (95% CI -\$5,791 to \$31,878), with only a 6.4% probability of cost-effectiveness at a \$50,000/QALY threshold (59). EGDT was associated with more intravenous fluids, vasopressor infusions (76% vs. 66%), red-cell transfusions (13.6% vs. 7.0%), and dobutamine use (15.4% vs. 2.6%) without improving organ failure scores or quality of life (5,6). These findings are particularly relevant for geriatric patients, who are more susceptible to complications from these interventions, though no age-specific data exist.

CONCLUSION AND RECOMMENDATIONS

Conclusions

This systematic review yields two definitive conclusions. First, for the general adult population with sepsis, Early Goal-Directed Therapy offers no mortality benefit compared to contemporary standard care in high-income healthcare settings. The three landmark trials (ProCESS, ARISE, ProMISe) and subsequent meta-analyses consistently demonstrate that EGDT's historical mortality benefit has been eroded by the incorporation of its core principles into routine sepsis management. EGDT remains associated with increased treatment intensity, higher costs, and no improvement in quality of life.

Second, and more critically, there is no evidence to support or refute the effectiveness of EGDT specifically in geriatric patients (aged ≥65 years) with sepsis. The complete absence of age-stratified analyses, age-treatment interaction tests, or separate effect estimates for elderly populations represents a fundamental evidence gap. The single study enrolling exclusively geriatric patients found that aggressive hemodynamic targeting increased mortality, raising legitimate concerns that protocolized resuscitation strategies designed for younger adults may be inappropriate—or even harmful—for older patients.

Recommendations

For clinical practice, EGDT should not be routinely implemented as a separate protocol in settings where standard care already includes early sepsis recognition, prompt antibiotics, appropriate fluid resuscitation, and vasopressor support. For geriatric patients specifically, clinicians should exercise caution when applying aggressive hemodynamic protocols, recognizing the absence of evidence and potential for harm suggested by limited data. Individualized, physiology-guided resuscitation with careful monitoring for complications (fluid overload, arrhythmias) is prudent.

For research, this review identifies a priority agenda. First, large, adequately powered randomized controlled trials comparing protocolized resuscitation to usual care specifically in patients ≥65 years are urgently needed. Second, existing datasets from ProCESS, ARISE, ProMISe, and other major trials should undergo post-hoc age-stratified analyses to generate hypotheses about age-treatment interactions. Third, geriatric-specific physiological targets (e.g., optimal MAP, fluid tolerance thresholds) require empirical determination rather than extrapolation from younger populations. Fourth, future sepsis trials must mandate prespecified subgroup analyses by age and report outcomes for geriatric patients separately. Without these efforts, the care of the majority of sepsis patients—older adults—will continue to be guided by evidence derived from younger populations, a practice that is both scientifically inadequate and potentially unsafe.

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