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Implementing Surviving Sepsis Campaign Guidelines and Mortality of Adult Patients in Intensive Care Units: An Integrative Review

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Abstract

Background: Sepsis is a common dangerous body response to infection that can deteriorate into septic shock. Both sepsis and septic shock require early and timely managed care, which can be implemented by using the Surviving Sepsis Campaign (SSC) guidelines for management of sepsis and septic shock. The purpose of this study was to examine the literature related to the effect of implementing SSC guidelines for management of sepsis and septic shock on adult patients' mortality rate in Intensive Care Units (ICUs). **Methods:** The method of Whittemore and Knafl was used to guide this integrative literature review. The literature search revealed 16 eligible quantitative research studies between 2004 and 2018. The quality of methods used in the included articles was assessed and data were analyzed. **Results:** Results showed that implementing SSC guidelines reduced the mortality rate among adult patients in ICUs. In addition, implementing selected practices from SSC guidelines, such as collecting blood cultures and administration of a broad-spectrum antibiotic and vasopressors were found to decrease the mortality rate among adult patients in ICUs. The SSC guidelines need to be taught to nurses and nursing students to increase their awareness and capability of implementing these guidelines in clinical practice.

Keywords

Sepsis, Septic Shock, Mortality, SSC, Guidelines

1. Introduction

Sepsis is a life-threatening illness. Every year it affects 30 million people globally [1] and 285 per 100,000 in Taiwan [2]. In Intensive Care Units (ICUs), sepsis

prevalence ranged from 10.5% to 37% in different countries, including France, Germany, the Netherlands, China, and Thailand [2] [3] [4] [5] [6]. In addition, sepsis and septic shock (SS) together were responsible for 25.4% of ICU admissions during one pilgrim season in Mecca [7].

Sepsis occurs as a dangerous response of the body to infection accompanied by organ dysfunction; it can cause systemic biologic, biochemical, and physiologic abnormalities [8]. Sepsis is characterized by having tachycardia, hypotension, hyperthermia or hypothermia, tachypnea, and leukocytosis or leukopenia. Signs of acute kidney failure, heart failure, and lung dysfunction may start to appear [9]. In cases where sepsis deterioration into SS may occur, patients will have hypotension and poor perfusion, and they will be unresponsive to intravenous fluids administration, making it necessary to administer vasopressors to manage hypotension [8].

Sepsis has negative consequences on health and health-care cost. It was found to be responsible for six million annual deaths around the world, [10] and 250,000 deaths annually in the USA alone [11]. Without proper and systematic management, sepsis can increase the mortality rate, [12] adding an additional $14 billion dollars to the overall global health expenditure [13]. Moreover, patients with sepsis have been found to have a greater risk of recurrent hospitalization [8] [14] and developing secondary infections later on during hospitalizations, such as pneumonia and bloodstream infections [15]. Fortunately, patients' bad prognosis can be prevented and the mortality rate can be decreased by early management of sepsis and SS [16]. For this reason, nurses must screen patients for sepsis, and sepsis management should be carried out as early as possible when sepsis is suspected [17].

Surviving Sepsis Campaign (SSC) guidelines are intended to provide guidance for the management of sepsis and SS [18]. These guidelines for the management of sepsis and SS were shown to reduce the mortality rate among patients in ICUs, significantly [12] [18] [19]. In Taiwan, Chou *et al*. (2014) [20] indicated that applying SSC guidelines also decreased the mortality rate from 34.6% to 24.5% among patients in ICU. Pestana *et al*. (2010) [21] conducted a retrospective study. The study results revealed that applying SSC guidelines decreased the mortality rate among 184 patients in ICUs ($p < 0.001$).

Nurses have a vital role in screening and early management of sepsis [22]. In Spain, a national educational program for nurses and physicians led to improvement in the care of patients with sepsis, improved compliance with sepsis management, and reduced mortality rate [23]. In addition, a nurse-driven sepsis management protocol can improve compliance with SSC guidelines and enhance early recognition of sepsis [24]. However, many nurses have poorly adhered to guidelines of sepsis diagnoses and management [25]. In any case, sepsis also occurs with other illnesses concurrently, which can be confusing [26].

Searching the different databases, no Integrative Literature Review (ILR) was conducted with the purpose of examining research literature that studied the ef-

fect of implementing SSC guidelines on adult patients' mortality rate in ICUs. The results of this ILR can help in presenting synthesized evidence, in addition to adding more information to the body of literature about the effect of implementing SSC guidelines on patients' mortality in ICUs. Moreover, having such information can help nurses and other healthcare providers in enhancing management of patients with sepsis and SS. This review will increase awareness of nursing administrators and educators about sepsis management based on SSC guidelines.

2. Method

2.1. Problem Identification

There are increasing research studies investigating the effect of implementing SSC guidelines for the management of sepsis and SS on adult patients' outcomes. The authors of this ILR identified the need to reach an in-depth understanding of this relationship. The purpose of this ILR was to examine the literature related to the effect of implementing the Surviving Sepsis Campaign (SSC) guidelines for the management of sepsis and SS on adult patients' mortality rate in ICUs.

The proposed method of Whittemore and Knafl (2005) [27] was used to guide this ILR and to improve its rigor. Whittemore and Knafl (2005) [27] modified the integrative literature review method of Cooper (1998) [28], which was composed of five stages: problem formulation; a search of literature; data evaluation; data analysis; and presentation of findings. This updated methodology for ILR enables the rigor to be enhanced. It also enhances data synthesis and combining studies with different methodologies in order to give a wide perspective on phenomena [27]. For the current ILR, this method was beneficial because studies with different methods were included.

2.2. Literature Search

The literature search was undertaken in November 2018 by using MEDLINE, Cab Direct, ProQuest Central, SpringerLink, CINAHL Plus, the Cochrane Database of Systematic Reviews, Scopus and Google Scholar. The following keywords were used in different combinations to guide the search: "sepsis", "septic shock", "surviving sepsis campaign", "guidelines", "bundle", "outcomes", "death", and "mortality". The search was conducted by entering the following words: surviving sepsis campaign AND guidelines AND mortality, surviving sepsis campaign AND guidelines AND death, surviving sepsis campaign AND bundle AND mortality, surviving sepsis campaign AND mortality, sepsis AND bundle AND mortality, septic shock AND bundle AND mortality; surviving sepsis campaign AND septic shock AND mortality. The inclusion criteria for research articles were: 1) Research studies published between 2004 and 2018, because the SSC guidelines for sepsis management were first published in 2004 [29] 2) Studies that investigated the effect of implementing SSC guidelines on adult patients' mortality in ICUs only, with no restriction for study design; 3) Articles written

in English.

2.3. Search Results

The initial search resulted in 729 articles. This search was carried out by the principal investigator. The titles and abstracts were reviewed based on the inclusion criteria to assess articles' eligibility. A total number of 334 research articles were duplicate, they were counted manually by name and frequency, and then duplicates were excluded. An additional 330 articles were excluded based on title and abstract information. The remaining 65 articles were retrieved as full-text and were assessed again for meeting the inclusion criteria; 36 of them were conducted in settings other than ICUs or in mixed settings, and 13 studies were ineligible reviews. Only 16 studies were eligible and the remaining 49 articles were excluded (see Figure 1).

The primary investigator used a research matrix to extract the required data (see Table 1). From each article, the following data were extracted: study purpose, design, settings, sample size, sampling technique, year of implementing the SSC guidelines, and main findings. In addition, the data extracted from the articles were used again to confirm eligibility of the included articles based on the

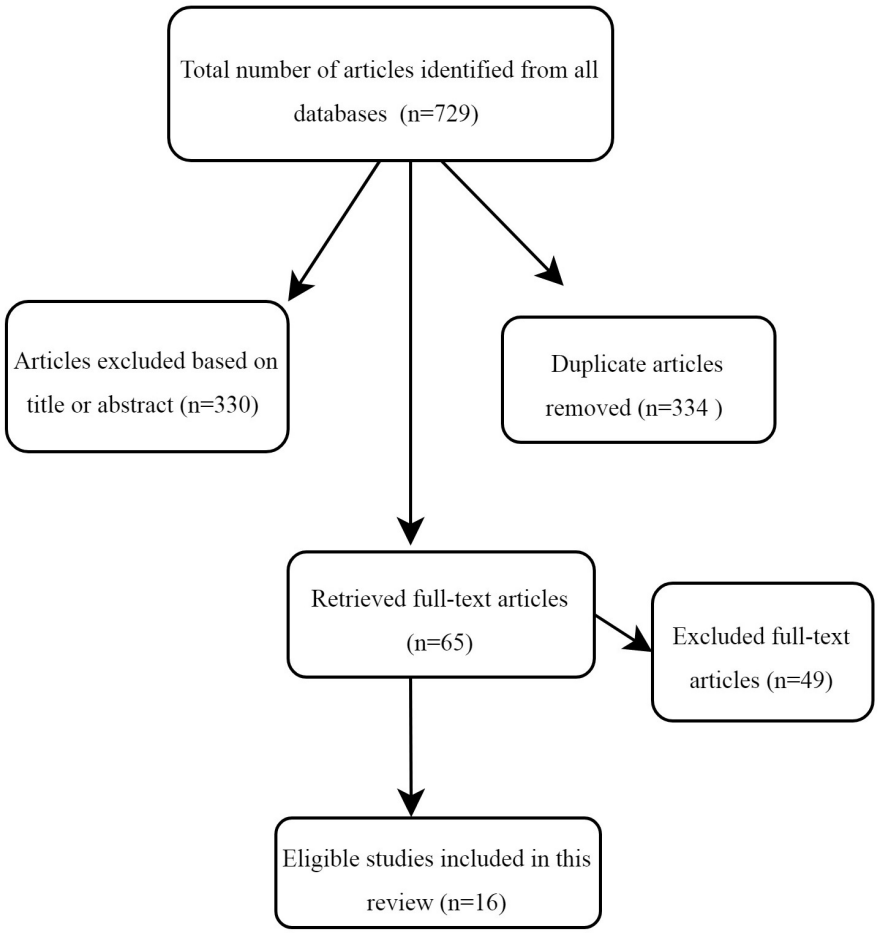

Figure 1. Flow diagram of study selection strategy.

Table 1. Study characteristics.

Authors	Purpose	Design	Settings	Sample size and sampling technique	Year of implementing the SSC guidelines	Main findings
Chou *et al.* (2014) [20]	To implement sepsis guidelines and examine their effect on patients with severe sepsis or septic shock in ICUs.	A prospective observational cohort design. The study had four phases: preintervention, education, operational and postintervention.	13-bed ICU in a tertiary medical center in southern Taiwan.	N = 164 Convenient	2010 to 2011	Implementation of the modified sepsis guidelines was successful in reduction of in-hospital mortality and hospital expenditure. In-hospital mortality rates were: 34.6% 10.0%, 23.1% and 24.5%, for Pre-intervention, education, operation and post-intervention phases, respectively ($p < 0.05$).
Pestana *et al.* (2010) [21]	To analyze the compliance with a sepsis guidelines and the impact of the fulfillment of different therapeutic guidelines on ICU survival in a cohort of surgical patients with septic shock.	Retrospective, observational descriptive design was used to consider compliance with seven quality indicators of sepsis bundle.	Surgical ICUs in two University hospitals in Spain.	N = 182 Convenient	2003 and 2008	ICU survival was significantly related to the number of fulfilled therapeutic guidelines included in a sepsis bundle. (OR, 1.64; 95% CI, 1.28 - 2.1; $p < 0.001$; survival was higher in the bundle-compliant patients. Mortality rates were 56.8% and 36.8% for patients not treated by bundle and those treated based on the bundle, respectively.

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Castella-nos-Ortega *et al.* (2010) [32]	To describe the effectiveness of the SSC guidelines with regard to both implementation and outcome in patients with septic shock, and to determine the contribution of the various elements of the guidelines to the outcome.	A quasi-experimental study that included a post intervention group and a historical comparison group. In addition, educational program based on the SSC guidelines was implemented over a 3 months period.	3 medical-surgical ICUs in an academic tertiary care center in Spain.	N = 384 Convenient	2005-2008	In-hospital mortality was reduced from 57.3% in the historical group to 37.5% in the intervention group ($p < 0.001$). The same happened with ICU mortality. The crude difference was (53.1% vs. 30.5%; $p < 0.001$) Improvements in survival were related to the number of interventions completed (p for trend <0.001).
Patel *et al.* (2010) [33]	To examine the effect of a collaborative 2-part sepsis guidelines on clinical outcomes and mortality at a community hospital.	Quasi-experimental. A multidisciplinary collaborative approach was adopted to conduct the study using retrospective and unblended data collection techniques.	An ICU in a non-academic community hospital 427-licensed bed for acute care in the USA.	N = 112 Convenient	2006	Mortality was 61.1% in the non-guidelines group versus 20% with the guidelines ($p < 0.001$). Implementation of a 2-part sepsis guidelines based on the SSC can yield a positive impact on clinical outcome and mortality.
Shiramizo *et al.* (2011) [34]	To determine the rate of compliance with 6-hour and 24-hour sepsis bundles, and to determine the impact of compliance on hospital mortality of patients with severe sepsis and septic shock.	Prospective quasi-experimental, pre and post design. Bundle compliance and patient outcomes were compared before (July 2005-April 2006) and after (May 2006-December 2009) implementation of the interventions.	medical-surgical ICU in a tertiary care private hospital in Sao Paulo, Brazil.	N = 564 Convenient	2006-2009	In-hospital mortality was 54.0% from July 2005 to April 2006, 41.1% from May to December 2006, 39.3% in 2007, 41.4% in 2008 and 16.2% in 2009. A statistically significant decreased OR for inpatients mortality was observed when

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						there was complete compliance with the 6-hour bundle (OR 0.54; CI 95% 0.30 - 0.96, p = 0.033) and when there was complete compliance with all of the components of the 24-hour bundle (OR 0.37; CI 95% 0.24 - 0.58, p < 0.001).
Cardoso *et al.* (2010) [35]	To evaluate the impact of compliance with a core version of the SSC 6-hour bundle on 28-day mortality.	Descriptive Cohort, multi-center, prospective study was conducted over one year. Patients were followed up until death or hospital discharge.	17 ICUs in Portugal.	N = 778 Consecutive	2004 to 2005	Compliance with all actions 1 to 6 was associated with an OR of 0.44 [95% CI = 0.24 - 0.80] in severe sepsis and 0.49 (95% CI = 0.25 - 0.95) in septic shock, for 28-days mortality. Collecting blood cultures and giving vasopressors were significantly protective.
Herrán-Monge *et al.* (2017) [36]	To determine the epidemiology and outcome of severe sepsis and septic shock after 9 years of the implementation of the SSC guidelines, and to build a mortality prediction model.	Quasi-experimental, Prospective, multicenter study was performed during a 5-month. Findings were compared with those obtained in the same ICUs in a study conducted in 2002.	11 medical/ surgical ICUs in 10 teaching hospitals in Spain.	N = 262 Convenient	2011	The 2011 cohort had a marked reduction in 48-hour (7% vs 14.8%), ICU (27.2% vs 48.2%), and in-hospital (36.7% vs 54.3%) mortalities. The implementation of the SSC guidelines resulted in a marked decrease in the overall mortality.

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Lefrant *et al.* (2010) [37]	To determine whether the implementation of 10 recommendations adapted from the SSC guidelines results in a reduction of mortality inpatients with severe sepsis and septic shock.	Quasi-experimental study that had two consecutive phases: a 6-month quality control period (observational) and secondly a 6-month intervention period.	15 ICUs in southern France.	N = 538 Consecutive	2006	The 28-day mortality rate significantly decreased from 40% in the observational period to27% in the intervention period (p = 0.02).
Leisman *et al.* (2017) [38]	To determine mortality and costs associated with adherence to an aggressive, 3-hour sepsis bundle versus noncompliance with greater than or equal to one bundle element for severe sepsis and septic shock patients.	Prospective, multisite, observational study used three sequential, independent cohorts, from a single USA health system, through their hospitalization.	Three cohorts in the USA: cohort 1: five tertiary and six community hospitals. Cohort 2: single tertiary academic medical center. Cohort 3: five tertiary and four community hospitals.	N = 14,755 (n1 = 5819, n2 = 1697, n3 = 7239) Consecutive	2010	In the three independent cohorts, 3-hour bundle compliance was associated with improved survival and cost savings. Mortality rate for compliant and non-compliant groups were: 21.3% and 25.4%, 13.4% and 17.8% and 18.1% and 21%, for cohorts 1, 2 and 3, respectively.
Memon *et al.* (2012) [39]	To assess the effect of improved compliance with the 6-hour sepsis resuscitation bundle on mortality of patients with severe sepsis and septic shock.	Quasi-experimental prospective design with a historical group as a control, and an intervention that was introduced over a 3-month period.	10-bedded combined medical and surgical ICU in a governmental hospital in Saudi Arabia.	N = 299 Consecutive	2009-2011	The overall compliance with 6-hour sepsis resuscitation bundle elements was associated with improved survival[OR, 5.8 (95% CI, 2.2 - 15.1; p < 0.001)]. 30-day hospital mortality reduced from 31.3% in the historical group to 21.1% in the intervention group; p = 0.05. There was a significant 30-day hospital mortality reduction in the post-intervention group.

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Miller III *et al.* (2013) [40]	To assess the effect on mortality of compliance with a severe sepsis and septic shock management guidelines.	An observational, retrospective, descriptive design was used. The study was conducted over three stages based on ICU admission date: (1) baseline and bundle development stage, (2) implementation stage, and (3) tracking stage.	18 ICUs in 11 hospitals in Utah and Idaho in the USA.	N = 4329 convenient	2004 and 2010	Severe sepsis and septic shock guidelines were associated with a marked reduction in hospital mortality after adjustment for age, severity of illness, and comorbidities. Relative mortality declined 59.0% from 21.2% at baseline to 8.7% for 2010 ($p < 0.0001$).
Sánchez *et al.* (2017) [41]	To analyze the evolution of sepsis-related mortality in Spanish ICUs following the introduction of the SSC guidelines and the relationship with sepsis process-of-care.	Quasi-experimental prospective cohort design was used. The study was conducted during two time periods: 2005 (Edusepsis study pre-intervention group) and 2011 (ABISS-Edusepsis study pre-intervention group).	41 medical-surgical ICUs in tertiary hospitals in Spain.	N = 1348 Consecutive	2005 to 2011	Patients in the interventional group had lower hospital mortality (32.6% vs. 44.0%; $p < 0.001$), lower 28-day mortality (23.0% vs. 36.5%; $p < 0.001$), and lower adjusted mortality (OR 0.64 [0.49 - 0.83], $p = 0.001$).
Thompson *et al.* (2016) [42]	To explore how the level of resuscitation guidelines adherence inhospitals influenced changes in outcomes of patients with sepsis and septic shock.	A quasi-experimental study compared patients with sepsis and septic shock in collaborative hospitals to other groups of patients in noncollaborative hospitals using the Michigan Inpatient Database.	87 Michigan hospitals with ICUs in the USA.	N = 48,110 Convenient	2012-2013	High adherence hospitals had significantly reduced in-hospital mortality between pre- and post-periods (35.0% vs 29.7%; $p < 0.001$), compared to non-collaborative hospitals. High adherence hospitals had significant reductions in mortality (OR, 0.84; 95% CI, 0.79 - 0.93; $p < 0.001$).

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van Zanten *et al.* (2014) [43]	To evaluate the effect of implementation of SSC bundles on adherence to the 6- and 24-hour sepsis bundle targets and adjusted in-hospital mortality.	Quasi-experimental, prospective, multicenter cohort in participating and nonparticipating centers.	82 ICUs in the Netherlands.	N = 16,418 Convenient	2009-2013	Adherence to sepsis bundles was associated with reduced adjusted in-hospital mortality only in participating ICUs, adjusted OR per month = 0.992 [0.986 - 0.997]) equivalent to 5.8% adjusted absolute mortality reduction over 3.5 years. A relative in-hospital mortality reduced by 16.7% over 3.5 years among patients in the ICUs.
Uvizl *et al.* (2016) [44]	To analyze the relationship between in-hospital mortality (either in ICU or after discharge from ICU) and the type and number of fulfilled diagnostic and treatment interventions during the first 6 hours after the diagnosis of severe sepsis/septic shock.	Multicenter, retrospective, observational study, which included all consecutive patients aged 18 and over who were admitted to participating ICUs from 1 January 2011 to 5 November 2013.	17 ICUs with a total of 220 beds in 12 hospitals in the Czech Republic.	N = 1082 Consecutive	2011-2013	The most effective measures associated with the lowest in-hospital mortality in patients with septic shock were CVP of ≥8 - 12 mm Hg, MAP of ≥65 mm Hg, urine output at ≥0.5 mL/kg/h, initial lactate level of ≤4.0 mmol/L and administration of antibiotics within the first hour.
Ferrer *et al.* (2009) [45]	To analyze the impact of treatments for severe sepsis on hospital mortality in all patients included in the three periods of the study (pre-educational period, post-educational period, and long-term follow-up).	Prospective, observational descriptive study that included three inclusion periods: a 2-month period before the implementation of an educational program, a 4-month period after its implementation, and a 2-month, long-term follow-up for 1 year.	77 ICUs in Spain.	N = 2804 Convenient	2006-2007	Early administration of broad-spectrum antibiotics in all patients reduce mortality.

Abbreviations: SSC: Surviving Sepsis Campaign; ICU: Intensive Care Unit; P: Power level or α; OR: Odd Ratio; CI: Confidence Interval; USA: United States of America; CVP: Central Venous Pressure; MAP: Mean Arterial Pressure; N: total sample size; n: sample size of a particular group; ScvO2: Central venous oxygen saturation; mm: millimol; ml: millileter; kg: Kiogram; h: hour; mmol: millimol; L: liter; mmHg: millimetre of mercury.

discussed eligibility criteria. Furthermore, the quality of the extracted data was checked by the second investigator by reading all of the 16 eligible articles and confirming the data of the research matrix. All of the 16 eligible articles are quantitative. Five of them were conducted in Spain, four studies were conducted in the USA, and the remaining seven studies were conducted in Portugal, France, Brazil, Saudi Arabia, Taiwan, the Netherlands, and the Czech Republic, with one study for each of the mentioned countries.

2.4. Data Evaluation, Rigor and Data Quality

The quality of methods used in the included articles was assessed by using criteria for assessing the quality of quantitative studies, which was recommended by Kmet *et al*. (2014) [30]. The criteria have 14 domains, for which the answers and scoring can be as follows: (Yes = 2); (Partially = 1); (No = 0); and not applicable. The quality score of each article was calculated by summing the total score of items and dividing it by the highest possible total score after removing non-applicable items [30]. The calculated summary score for each article can range between zero and two (see **Table 2**). This assessment was confirmed by the two other researchers.

2.5. Data Analysis

Based on Whittemore and Knafl's (2005) [27] method of ILR, analysis has four phases: 1) Data reduction: classifying and dividing data into subgroups; 2) Data display: showing data as they appeared in the research matrix (data extraction sheet), in order to enhance comparison; 3) Data comparison: examining data to identify pattern, relationships, and themes, by which variables can be grouped together and a conceptual map can be drawn; 4) Conclusion drawing and verification: by collecting the different parts that make up the whole general picture and verifying them, followed by synthesizing data and data integration. However, in order to use a more rigorous and well-described process of data analysis, inductive content analysis was used in addition to step number three above, as described by Elo and Kyngäs (2008) [31]. This included: coding, categorizing, collecting categories into higher order headings to decrease the number of headings, and finally abstracting by making a general description of the findings.

3. Results

The reviewed articles revealed that implementing SSC guidelines can reduce mortality rate among adult patients in ICUs [20] [21] [32]-[43]. It was shown that implementing the SSC guidelines reduced the mortality rate among adult patients in ICU from 54.0% to 16.2% (N = 564) [34], from 35.0% to 29.7% ($p < 0.001$) (N = 48110) [42], and from 56.8% to 36.8% [21]. In addition, implementing the SSC guidelines was associated with improved patient survival [odds ratio (OR), 5.8 (95% CI, 2.2 - 15.1; $p < 0.001$)] [39] with relative mortality rate declined from 21.2% to 8.7% ($p < 0.0001$) [40].

Table 2. Quality and rigor of the eligible studies.

Item	Chou *et al.* (2014) [20]	Pestana *et al.* (2010) [21]	Castellanos-Ortega *et al.* (2010) [32]	Patel *et al.* (2010) [33]	Shiramizo *et al.* (2011) [34]	Cardoso *et al.* (2010) [35]	Herrán-Monge *et al.* (2017) [36]	Lefrant *et al.* (2010) [37]	Leisman *et al.* (2017) [38]	Memon *et al.* (2012) [39]	Miller III *et al.* (2013) [40]	Sánchez *et al.* (2017) [41]	Thompson *et al.* (2016) [42]	van Zanten *et al.* (2014) [43]	Uvizl *et al.* (2016) [44]	Ferrer *et al.* (2009) [45]
Question/objective sufficiently described?	1	1	2	2	1	1	1	1	1	1	1	2	2	1	1	1
Study design evident and appropriate?	2	1	1	1	2	2	1	1	2	1	1	2	2	1	1	1
Method of subject/comparison group selection or source of information/input variables described and appropriate?	1	1	2	1	1	1	1	1	1	1	1	2	2	2	1	2
Subject (and comparison group, if applicable) characteristics sufficiently described?	1	2	2	1	2	1	2	1	2	1	2	2	2	2	2	2
If interventional and random allocation was possible, was it described?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
If interventional and blinding of investigators was possible, was it reported?	NA	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA
If interventional and blinding of subjects was possible, was it reported?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/misclassify cation bias? Means of assessment reported?	2	1	2	2	1	1	1	1	1	2	1	2	1	2	2	2
Sample size appropriate?	0	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2
Analytic methods described/justified and appropriate?	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1

Continued

Some estimate of variance is reported for the main results?	1	2	1	2	2	2	2	2	2	1	2	1	2	0	2	2
Controlled for confounding?	0	0	0	0	1	1	1	1	0	0	0	1	0	1	1	0
Results reported in sufficient detail?	2	2	1	2	2	2	1	2	2	1	2	2	2	2	2	2
Conclusions supported by the results?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Summary Score	0.60	0.68	0.73	0.64	0.77	0.77	0.68	0.68	0.71	0.60	0.68	0.86	0.86	0.73	0.77	0.77

3.1. SSC Guidelines and In-Hospital Mortality

Implementing SSC guidelines were found to reduce in-hospital mortality rates [20] [40] [41] [42] [43]. Specifically, in-hospital mortality was reduced from 57.3% to 37.5% ($p < 0.001$) (N = 384) [32], from 44.0% to 32.6% ($p < 0.001$) (N = 1348) [41], from 61.1% to 20% ($p < 0.001$) (N = 112) [33], 35.0% to 29.7% ($p < 0.001$) [42], and from 54.3% to 36.7% [36]. Furthermore, in-hospital mortality was reduced in ICUs by 5.8% over 3.5 years, with a relative in-hospital mortality reduction of 16.7% among adult patients with sepsis and SS in ICUs compared to baseline [43].

3.2. SSC Guidelines, 28-Day Mortality, 30-Day Mortality, and ICU Mortality

Implementing SSC guidelines reduced 28-day mortality among adult patients in ICUs [35] [37] [41], from 40% to 27% ($p = 0.02$) (N = 538) [37], and from 36.5% to 23.0% ($p < 0.001$) (N = 1384) [41], with odds ratio (OR) of 0.44 [95% confidence interval (CI) = 0.24 - 0.80] in sepsis and 0.49 (95% CI = 0.25 - 0.95) for association of implementing the SSC guidelines with 28-day mortality [35]. Similarly, 30-day mortality was reduced from 31.3% to 21.1% ($p = 0.05$) [39]. In addition, implementing the SSC guidelines reduced ICU mortality rates [21] [32] [36], from 48.2% to 27.2% ($p < 0.01$) [36], from 53.1% to 30.5% ($p < 0.001$) [32], and from 56.8% to 36.8% ($p = 0.036$) [21].

3.3. Certain Selected Guidelines and Patient Mortality

Two studies investigated the effect of implementing certain practices selected from the SSC guidelines, such as the administration of antibiotics, which was found to decrease the mortality rate [44] [45]. Specifically, the risk of mortality in the case of administering a broad-spectrum antibiotic during the first hour of sepsis compared with no antibiotic in the first 6 hours had an odds ratio [OR] of 0.67; 95% confidence interval [CI], 0.50 - 0.90; $p < 0.01$) [45]. In addition, collecting blood cultures and giving vasopressors decreased the mortality rate among adult patients with sepsis and septic shock in ICUs [35]. Castellanos-

Ortega *et al*. (2010) [32] pointed out that an inverse relationship exists between mortality rate and the number of implemented SSC guidelines for the management of septic shock. In more detail, the mortality rate was significantly related to the number of accomplished therapeutic guidelines, with an odds ratio [OR] of 1.64; 95% confidence interval [CI], 1.28 - 2.1 ($p < 0.001$) [21].

4. Discussion

Common themes that emerged from this ILR were: First, implementing the SSC guidelines can decrease the mortality rate among adult patients with sepsis and SS in ICUs; this corresponds to the findings of Lefrant *et al*. [37], Leisman *et al*. [38], Patel *et al*. [33], Pestana *et al*. [21], Cardoso *et al*. [35], Memon *et al*. [39], Sánchez *et al*. [41], Thompson *et al*. [42], van Zanten *et al*. [43], and Levy *et al*. [12]. The second emerged theme was that implementing certain selected guidelines, such as collecting blood cultures and administering broad-spectrum antibiotics and vasopressors can also reduce the mortality rate among adult ICU patients, which was consistent with the findings of Uvizl *et al*. [44] and Ferrer *et al*. [45]. The calculated scores for rigor of the research articles ranged between 0.60 and 0.86, with a mean average of 0.72 ± 0.078. The distribution of scores on histogram was close to normal distribution with skewness level of 0.26. A cut-point score of 0.75 is conservative, while a cut-point score of 0.55 is liberal [30]. However, the minimum score of the included studies was 0.60 indicating adequate rigor of the included studies; therefore, no studies were excluded based on the calculated scores.

There are some limitations of the reviewed studies. Out of the 16 eligible articles, six research articles were descriptive in nature, while the remaining ten research articles used a quasi-experimental design. However, for the discussed clinical problem, quantitative studies are the type of study expected to investigate the research problem in a suitable way. However, the sample size was small in the observational study of Pestana *et al*. [21], which may limit its generalizability. The studies of van Zanten *et al*. [43], Thompson *et al*. [42], Uvizl *et al*. [44], Sánchez *et al*. [41], and Leisman *et al*. [38], recruited large numbers of participants. Moreover, the studies of Ferrer *et al*. [45], Castellanos-Ortega *et al*. [32], Patel *et al*. [33], Shiramizo *et al*. [34], Thompson *et al*. [42], Chou *et al*. [20], and Herrán-Monge *et al*. [36] used convenient samples of patients, which might have carried a risk of sampling bias [46]. Furthermore, the studies of Pestana *et al*. [21], Miller III *et al*. [40], and Uvizl *et al*. [44] used a retrospective observational research design, which might not be a robust design to be used for answering such research question.

Some possible confounding variables were not controlled in some studies. For example, the variable of baseline severity of patients' illness was not measured in the study by Thompson *et al*. [42]. In addition, around half of the included patients in the study by Pestana *et al*. [21] were patients with cancer, which might limit the generalizability of the study. The reviewed studies came from a wide

variety of countries where healthcare and implementation practices likely differ, and the populations were different also. In addition, the implemented guidelines were belonging to the period between 2004 and 2013, which indicate different updates of the guidelines. These differences might explain some of the variability in the results.

5. Conclusions

The reviewed articles revealed that implementing SSC guidelines for adult patients with sepsis and SS in ICUs has decreased mortality rates. The findings of the current ILR imply that nurses and physicians working in multidisciplinary teams at ICUs are required to implement the guidelines of SSC while providing care for adult patients with sepsis and SS. Educational campaigns and continuous learning programs are needed to teach nurses about the importance of implementing the SSC guidelines and how to implement them. Moreover, internal audit teams can be formed to evaluate nurses' compliance with the SSC guidelines for managing patients with sepsis and SS in ICUs. Furthermore, the SSC guidelines need to be taught to nursing students to increase their awareness and capability of implementing these guidelines in clinical practice.

All of the eligible studies included in the current ILR were conducted between 2004 and 2013, so studying the effect of implementing the newly released guidelines of SSC 2016 and 2018 for the management of sepsis and SS on adult patients' mortality is recommended. The findings of this ILR need to be considered by administrators and policymakers in order to integrate the SSC guidelines of sepsis management during providing care for patients in ICUs. Future studies that may seek to investigate the same problem need to take into consideration using more rigorous research designs, such as the use of randomized allocation of participants and blinding techniques.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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