**International Guidelines for Management of Sepsis and Septic Shock**

**Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2021**

# METHODOLOGY

## Guidelines Scope

The Surviving Sepsis Campaign (SSC) guidelines provide recommendations to support clinicians managing adult patients in a hospital setting with, or at risk of developing, sepsis or septic shock. The target users of these guidelines are frontline clinicians, allied health professionals, and policymakers involved in the care of patients with sepsis or septic shock. The guidelines apply mostly to high income settings, but we discuss the adaptation of these recommendations to low-middle income settings where data allow. Sepsis bundles are structured quality improvement tools intended to facilitate process improvement and patient outcomes. In addition to clinical practice guidelines, SSC has developed sepsis bundles. The SSC bundles are developed through a process distinct from the guidelines and may be useful as a tool to implement the SSC guideline recommendations. The Hour-1 bundle was developed and published in 2018 for this purpose.

## Definitions

These guidelines used the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (1). *Sepsis* is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. *Septic shock* is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (5). While Sepsis-3 definitions also included clinical criteria for sepsis and septic shock, most studies comprising the evidence for these guidelines, including all those published prior to 2016, used earlier definitions of sepsis, severe sepsis, and septic shock (6).

## History of the Guidelines

These guidelines are a revision of the 2016 SSC guidelines for the management of sepsis and septic shock (7, 8). The first SSC guidelines were published in 2004 (9), revised in 2008 (10, 11) 2012 (7, 8), and 2016 (12, 13). This current iteration describes evidence that was obtained from literature through to July 2019. The Children’s’ SSC guidelines have been published separately by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) (14, 15).

## Sponsorship

The sponsoring societies, SCCM and ESICM, funded the development of these guidelines. In addition, sponsoring organizations provided support for their members’ involvement. No funding (or influence) was derived from the healthcare industry.

## Selection and Organization of Committee Members

Two co-chairs and two co-vice-chairs were appointed by the SCCM and ESICM governing bodies. The co-chairs brought together a panel that combined committee members with expertise in specific aspects of sepsis, representatives from sponsoring organizations and 11 members of the public who were able to provide the patient’s perspectives into the process. Panel members were selected to obtain a balance of expertise, gender, geographic location, and economic region, and to balance continuity and provide new perspectives with the previous committees’ membership as well as to address content needs.

The SSC panel, from 22 countries, included academic specialists in critical care medicine, emergency medicine, infectious diseases, nursing, allied health, clinical pharmacy, and experts in research methodology. The *Guidelines in Intensive Care Development and Evaluation* (GUIDE) group provided methodological support, including systematic reviews, throughout the guideline development process.

The SSC panel was divided into six groups: screening and initial resuscitation, infection, hemodynamics, ventilation, additional therapies, and goals of care and long-term outcomes. Each group had at least one representative from a low- or middle-income country.

Management of Conflict of Interests
There was no industry input into the guidelines development and no industry representatives attended any of the meetings. No member of the guidelines committee received honoraria for any role in the guidelines process. The management of potential conflicts of interest (COI) was overseen by a COI committee, co-chaired by one ESICM appointee and one SCCM appointee, with a process that relied on personal disclosure and then management of any potential conflicts as seen relevant by the committee. Disclosure of both potential financial and potential intellectual COI was made. All disclosures were reviewed prior to panelists commencing work and influenced panel sub-group assignment. They were then updated at intermittent times throughout the process and again prior to publication of the manuscript. Significant potential COIs were managed by altering group assignment and recusal from voting on a recommendation relevant to the potential conflict. Potential conflicts that were deemed non-resolvable would have been managed by excluding the participant from panel membership, however there were no potential conflicts deemed unresolvable.

## Question Development

The guideline development process is summarized in **Figure S1**. Topic selection was the responsibility of the co-chairs and group heads, with input from the methodologists and guideline panel. Prioritization of the topics and questions was done within each of the six groups using a framework incorporating: 1) panel rating scores, 2) clinical practice variability, and 3) inclusion of the topic or question in a previous version of the guidelines.

All guideline questions were structured in the Population, Intervention, Control, and Outcome(s) (PICO) format, with explicit definition of each domain.

## Outcome Prioritisation

We used the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach to identify outcomes that we considered important from a patient’s perspective (16). For each question, the panel developed a list of relevant outcomes, then electronically voted on the importance of each outcome from a patient perspective. Mean scores were used to select critical and important outcomes. All PICO-questions with supporting evidence are presented in Supplemental Digital Content Appendices 1-6. Patient and family representatives participated in outcome prioritization.

Patient Engagement
Eleven patient and family representatives from different countries and backgrounds worked directly with the goals of care & long-term outcomes group, given the value-laden nature of these recommendations. For this group, the patient and family representatives helped to develop and rate the outcomes for each question, reviewed evidence summaries, and provided input on recommendations. Additionally, they worked with other groups on an ad hoc basis and commented on specific questions. Finally, they participated in separate teleconferences with the Co-Vice-Chairs where they shared their experience as sepsis patients/caregivers and provided feedback on the process of the guideline development process.

## Literature Search

Professional librarians drafted and executed a literature search for each defined question or group of relevant questions. Panel members worked with group leads, methodologists, systematic review teams, and librarians to identify pertinent search terms that included, at a minimum, sepsis, severe sepsis, septic shock, sepsis syndrome and critical illness combined with appropriate question-specific keywords. Searches were restricted to English language. The search strategy is available in Supplemental Digital Content Appendix 7.

For PICO questions addressed in the 2016 SSC guidelines, the search strategy was updated and rerun from the date of the previous literature search. For each of the new questions, an electronic search was conducted of a minimum of two major bibliographic databases (MEDLINE, and EMBASE), and three databases of clinical trials (Cochrane Central, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform) to identify relevant systematic reviews and randomized clinical trials (RCTs). For some questions, we searched for systematic reviews on the Epistemonikos systematic reviews database (<https://www.epistemonikos.org/en/>) and/or the Cochrane Database of Systematic Reviews. Additional databases such as CINAHL, PsycInfo were searched as appropriate for some questions, for example the PICO questions about long term outcomes. Validated search filters for RCTs, observational studies, guidelines or systematic reviews from the Canadian Agency for Drugs and Technologies in Health (CADTH) were incorporated into the search strategy when required. Search results were imported into reference management software (EndNote), deduplicated, and imported into Covidence for screening.

## Selection of studies and data abstraction

For all PICO questions, methodologists and panelists screened titles and abstracts retrieved from the bibliographic databases. The selection process aimed to identify the most recent, highest quality evidence. Therefore, recently published systematic reviews of RCTs were sought. Individual relevant RCTs and observational studies were identified for PICO questions without relevant systematic reviews, and to capture more recent publications not included in systematic reviews. Additionally, content experts identified any studies not captured by the search. Studies were assessed for eligibility according to pre-specified criteria related to the components of the corresponding PICO question. When a meta-analysis update or a new analysis was required, the SRT abstracted relevant data from eligible studies, and items relevant to risk of bias assessment. Intention-to-treat data were used whenever available; otherwise, complete case data, ignoring missing data were used (17).

Table S1. Description of implications of strength of recommendation for patients, clinicians and policymakers.

|  |  |  |
| --- | --- | --- |
|  | **Strong Recommendation** | **Weak Recommendation** |
| For patients | Most individuals would want the recommended course of action.   A small proportion would not. | The majority of individuals would want the suggested course of action but many would not. |
| For clinicians | Most individuals should receive the recommended course of action.  | Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient’s circumstances. |
| For policy makers | The recommendation can be adapted as policy in most situations, including use as performance indicators | Policy-making will require substantial debates and involvement of many stakeholders. |

## Analysis

When conducting a meta-analysis, DerSimonian and Laird random-effects models (18) to pool weighted effect sizes across studies were used. Pooled estimates were reported as relative risk (RR) or odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes; and mean difference (MD) with 95% CI for continuous outcomes. Heterogeneity between studies was assessed using the Chi2 statistic (*P* < 0.01 indicating substantial heterogeneity) and the I2 statistic (> 50% indicating substantial heterogeneity), and by inspecting forest plots.

## Quality of evidence and Grading of Recommendations

Methodologists in each subgroup, with input from designated panel members, used the GRADE approach to assess the quality of evidence (19) and summarize confidence in the estimate of the effect to support a recommendation (20) [Table S1]. The quality of evidence was rated as high, moderate, low, or very low (21). The guideline development tool (GDT) online software (http://gdt.guidelinedevelopment.org) was used to generate evidence profiles (evidence summaries) (22). The quality of evidence informed the strength of recommendations (19). The GRADE approach is based on assessing the evidence according to six domains: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, 5) publication bias, and 6) other criteria. RCTs begin as high-quality evidence that can be downgraded due to limitations in any of the domains. While observational (nonrandomized) studies begin as low-quality evidence, the quality level can be upgraded based on a large magnitude of effect or other factors.

## Recommendation Formulation

The evidence-to-decision framework (EtD) was used to formulate recommendations, with each of the six groups drafting the preliminary recommendations that were reviewed and voted upon by the entire panel (23). The EtD framework covered the following domains: priority setting, magnitude of benefit and harm, certainty (i.e., quality) of the evidence, patient values, balance between desirable and undesirable effects, resources and cost, equity, acceptability, and feasibility. Using the EtD framework, the guideline panel assessed whether the desirable effects of an intervention would outweigh the undesirable effects, and the strength of a recommendation reflects the panel’s degree of confidence in that balance assessment. Thus, a strong recommendation in favour of an intervention reflects the panel’s opinion that the desirable effects of adhering to a recommendation will clearly outweigh the undesirable effects. A weak recommendation in favour of an intervention indicates the judgment that the desirable effects will likely outweigh the undesirable effects.

We use the wording “we recommend” for strong recommendations and “we suggest” for weak recommendations (12, 13). Best practice statements (BPSs) appear throughout the document; these statements represent ungraded strong recommendations and are applied using strict criteria (24). A BPS would be appropriate, for example, when the benefit or harm is unequivocal, but the evidence is hard to summarize or assess using GRADE methodology.

## In Our Practice Statements

In this version of the SSC guidelines, we introduce a new category of statements: *in our practice statements*. These statements are not recommendations and are only meant to represent the practice of the majority of the SSC panel when there is insufficient evidence to support a recommendation. We surveyed the panel to formulate these statements when there was insufficient evidence to provide guidance on a question.

## Voting Process

Following formulation of preliminary recommendations and BPSs, face-to-face meetings were held in December 2019 and February 2020, where the groups presented their draft recommendations and received input and feedback from the full panel. Revised recommendations incorporating the feedback were sent for electronic voting. Although all panel members received links to polls using Survey Monkey, Inc. (Palo Alto, CA); only non-conflicted panel members were permitted to vote on individual question. Panel members had to indicate agreement, disagreement, or abstention with the recommendation. Acceptance of a recommendation required 80% agreement threshold as agreed *a priori* prior to voting commencing with at least 75% of the panel voting. Voters could provide feedback for consideration in revising statements that did not receive consensus in up to three rounds of voting.