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

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

Laura Evans1, Andrew Rhodes2, Waleed Alhazzani3, Massimo Antonelli4, Craig M Coopersmith5, Craig French6, Flávia R. Machado7, Lauralyn Mcintyre8, Marlies Ostermann9, Hallie C. Prescott10, Christa Schorr11, Steven Simpson12, W Joost Wiersinga13, Fayez Alshamsi14, Derek C. Angus15, Yaseen Arabi16, Luciano Azevedo17, Richard Beale18, Gregory Beilman19, Emilie Belley-Cote20, Lisa Burry21,  Maurizio Cecconi22, John Centofanti23, Angel Coz Yataco24, Jan De Waele25, R. Phillip Dellinger26, Kent Doi27, Bin Du28, Elisa Estenssoro29, Ricard Ferrer30, Charles Gomersall31, Carol Hodgson32, Morten Hylander Møller33, Theodore Iwashyna34, Shevin Jacob35, Ruth Kleinpell36, Michael Klompas37, Younsuck Koh38, Anand Kumar39, Arthur Kwizera40, Suzana Lobo41, Henry Masur42, Steven McGloughlin43, Sangeeta Mehta44, Yatin Mehta45, Mervyn Mer46, Mark Nunnally47, Simon Oczkowski48, Tiffany Osborn49, Elizabeth Papathanassoglou50, Anders Perner51, Michael Puskarich52, Jason Roberts53, William Schweickert54, Maureen Seckel55, Jonathan Sevransky56, Charles L Sprung57, Tobias Welte58, Janice Zimmerman59, Mitchell Levy60.

**Affiliations**

Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, USA

Adult Critical Care, St George’s University Hospitals NHS Foundation Trust & St George’s University of London, London, UK

Department of Health Research Methods, Evidence, and Impact, McMaster University, Canada & Department of Medicine, McMaster University, Hamilton, Canada

Dipartimento di Scienze dell’ Emergenza  Anestesiologiche e della Rianimazione, Policlinico Universitario A. Gemelli IRCCS  Rome, Italy

Emory University School of Medicine, USA

Western Health, Melbourne, Australia

Federal University of Sao Paulo, Sao Paulo, Brazil

Ottawa Hospital, Ottawa, ON, Canada

Guy’s & St Thomas’ Hospital, London, England, UK

University of Michigan and VA Center for Clinical Management Research, USA

Cooper Health System, Camden, NJ, USA

University of Kansas Medical Center, Kansas City, KS, USA

1. Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis

Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates

University of Pittsburgh Critical Care Medicine CRISMA Laboratory, Pittsburgh, PA, USA

Intensive Care Department, Ministry of National Guard Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia

University of Sao Paulo, School of Medicine, Brazil

Guy’s & St Thomas’ Hospital, London, England, UK

University of Minnesota

Population Health Research Institute, Hamilton, Canada

Mount Sinai Hospital & University of Toronto (Leslie Dan Faculty of Pharmacy), Ontario Canada

Department of Anesthesia and Intensive care, Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

Department of Anesthesia, McMaster University, Hamilton, Canada

Lexington Veterans Affairs Medical Center / University of Kentucky College of Medicine

Ghent University Hospital, Ghent, Belgium

Cooper Health System, Camden, NJ, USA

The University of Tokyo, Japan

Medical ICU, Peking Union Medical College Hospital, 1 Shuai Fu Yuan, Beijing 100730

Hospital Interzonal de Agudos San Martin de La Plata, Buenos Aires, Argentina

Intensive Care Department, Vall d'Hebron University Hospital, Vall d’Hebron Institut de Recerca. Barcelona, Spain.

Prince of Wales Hospital, Hong Kong, China

Australian and New Zealand Intensive Care Research Centre, Monash University, Australia

Copenhagen University Hospital Rigshospitalet, Department of Intensive Care 4131, Copenhagen, Denmark

University of Michigan Health System, USA

Liverpool School of Tropical Medicine, UK

Vanderbilt University Nashville TN, USA

Department of Medicine, Brigham and Women's Hospital, Boston MA; Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston MA, USA

ASAN Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

University of Manitoba, Winnipeg, MB, Canada

Makerere University College of Health Sciences, Uganda

Intensive Care Division. Faculdade de Medicina de São José do Rio Preto, São Paulo- Brazil

Critical Care Medicine department, NIH Clinical Center, Bethedsa, MD, USA

Alfred Health, Australia

Mount Sinai Hospital, Toronto, ON, Canada

Medanta The Medicity, Gurugram, Haryana, India

Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

New York University School of Medicine, New York, NY, USA

Department of Medicine, McMaster University, Hamilton, Canada

Washington University School of Medicine, St. Louis, MO, USA

Faculty of Nursing, University of Alberta, Edmonton AB, Canada

Rigshospitalet, Copenhagen, Denmark

University of Minnesota / Hennepin County Medical Center

University of Queensland Centre for Clinical Research, Faculty of Medicine The University of Queensland, Brisbane, Australia, Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Australia, Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes France

University of Pennsylvania, USA

ChristianaCare, Newark, DE, USA

Emory University School of Medicine, USA

Faculty of Medicine, Hebrew University of Jerusalem, Israel and Department of Anesthesiology, Critical Care and Pain Medicine, Hadassah Medical Center, Jerusalem, Israel

Medizinische Hochschule Hannover and German Center of Lung Research (DZL), Germany

World Federation of Intensive and Critical Care, Brussels, Belgium

1. Warren Alpert School of Medicine at Brown University, Providence, Rhode Island & Rhode Island Hospital, Providence, Rhode Island.

# ENDORSEMENTS

This manuscript has been endorsed by the following societies:

* European Society of Intensive Care Medicine
* Society of Critical Care Medicine
* American Association of Critical Care Nurses
* American College of Chest Physicians
* American College of Emergency Physicians
* American Thoracic Society
* African Sepsis Alliance
* Asia and Pacific Sepsis Alliance
* Association De Medicina Intensiva Brasileira
* Australian and New Zealand Intensive Care Society
* Canadian Critical Care Society
* Chinese Society of Critical Care Medicine
* Chest
* European Respiratory Society
* European Society of Clinical Microbiology and Infectious Diseases
* European Society of Intensive Care Medicine
* Indian Society of Critical Care Medicine
* Infectious Diseases Society of North America
* Japanese Society of Intensive Care Medicine
* Latin American Sepsis Institute
* Society for Academic Emergency Medicine
* Society of Critical Care Medicine
* Scandinavian Critical Care Trials Group
* Surgical Infection Society
* World Federation of Critical Care Nurses
* World Federation of Societies of Intensive and Critical Care Medicine

# ACKNOWLEDGEMENTS

It is with great appreciation that we acknowledge the public panel members who shared their insights and experiences as patients/relatives and provided advice which was invaluable to informing the updated guideline. Specifically, we thank: Dana Mirman, sepsis survivor & member of the Board of Directors of Sepsis Alliance, Idelette Nutma and Marie Mach, and 3 additional public panel members.

# GOVERNANCE OF SURVIVING SEPSIS CAMPAIGN

**SSC Guidelines Committee Co-chairs**

Andrew Rhodes, Laura Evans.

**SSC Guidelines Committee Co vice-chairs**

Hallie Prescott, Marlies Ostermann

**SSC Guidelines Committee Oversight Group**

Andrew Rhodes, Laura Evans, Waleed Alhazzani

**SSC Guidelines Committee Group-heads**

Craig French, Flavia Machado, Mitchell Levy, Lauralyn McIntyre, Christa Schorr, Steven Simpson, Joost Wiersinga.

**SSC Conflicts of Interest Co-chairs**

Massimo Antonelli, Craig Coopersmith

**GUIDE Methodology group**

Waleed Alhazzani (chair),

Emilie Belley-Cote

Fayez Alshamsi

John Centofanti

Mark Nunnally

Morten Hylander-Moller

Simon Oczkowski

# ABSTRACT

**Background**

Sepsis poses a global threat to millions of lives. The Surviving Sepsis Campaign (SSC) guidelines provide evidence-based recommendations on the recognition and management of sepsis and its complications.

**Methods**

We formed a panel of 60 experts from 22 countries and 11 members of the public. The panel prioritized questions that are relevant to the recognition and management of sepsis and septic shock in adults. New questions and sections were addressed, relative to the previous guidelines. These questions were grouped under 6 subgroups (screening and early treatment, infection, hemodynamics, ventilation, additional therapies, and long-term outcomes and goals of care). With input from the panel and methodologists, professional medical librarians performed the search strategy tailored to either specific questions or a group of relevant questions. A dedicated systematic review team performed screening and data abstraction when indicated. For each question, the methodologists, with input from panel members, summarized the evidence assessed and graded the quality of evidence using the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach. The panel generated recommendations using the evidence-to-decision framework. Recommendations were either strong or weak, or in the form of best practice statements. When evidence was insufficient to support a recommendation, the panel was surveyed to generate “in our practice” statements.

**Results**

The SSC panel issued 93 statements: 15 best practice statements, 15 strong recommendations, and 54 weak recommendations and no recommendation was provided for 9 questions. The recommendations address several important clinical areas related to screening tools, acute resuscitation strategies, management of fluids and vasoactive agents, antimicrobials and diagnostic tests and the use of additional therapies, ventilation management, goals of care, and post sepsis care.

**Conclusion**

The SSC panel issued evidence-based recommendations to help support key stakeholders caring for adults with sepsis or septic shock and their families.

Table of Contents

[ENDORSEMENTS 3](#_Toc77598631)

[ACKNOWLEDGEMENTS 4](#_Toc77598632)

[GOVERNANCE OF SURVIVING SEPSIS CAMPAIGN 5](#_Toc77598633)

[ABSTRACT 6](#_Toc77598634)

[Legend of tables 11](#_Toc77598635)

[INTRODUCTION 12](#_Toc77598636)

[METHODOLOGY 12](#_Toc77598637)

[Guidelines Scope 12](#_Toc77598638)

[Definitions 12](#_Toc77598639)

[History of the Guidelines 13](#_Toc77598640)

[Sponsorship 13](#_Toc77598641)

[Selection and Organization of Committee Members 13](#_Toc77598642)

[Management of Conflict of Interests 13](#_Toc77598643)

[Question Development 14](#_Toc77598644)

[Outcome Prioritisation 14](#_Toc77598645)

[Patient Engagement 14](#_Toc77598646)

[Literature Search 15](#_Toc77598647)

[Selection of studies and data abstraction 15](#_Toc77598648)

[Analysis 17](#_Toc77598649)

[Quality of evidence and Grading of Recommendations 17](#_Toc77598650)

[Recommendation Formulation 17](#_Toc77598651)

[In Our Practice Statements 18](#_Toc77598652)

[Voting Process 18](#_Toc77598653)

[Arrow up implies strengthening of recommendation and arrow down weakening. 28](#_Toc77598654)

[SCREENING AND EARLY TREATMENT 33](#_Toc77598655)

[Screening for patients with sepsis and septic shock 33](#_Toc77598656)

[Initial Resuscitation 35](#_Toc77598657)

[Mean Arterial Pressure 38](#_Toc77598658)

[Admission to Intensive Care 39](#_Toc77598659)

[INFECTION 40](#_Toc77598660)

[Diagnosis of infection 40](#_Toc77598661)

[Time to antibiotics 41](#_Toc77598662)

[Biomarkers to start antibiotics 43](#_Toc77598663)

[Antimicrobial choice 44](#_Toc77598664)

[Antifungal therapy 47](#_Toc77598665)

[Antiviral therapy 51](#_Toc77598666)

[Delivery of antibiotics 51](#_Toc77598667)

[Pharmacokinetics and pharmacodynamics 52](#_Toc77598668)

[Source control 56](#_Toc77598669)

[De-escalation of antibiotics 57](#_Toc77598670)

[Duration of antibiotics 58](#_Toc77598671)

[Biomarkers to discontinue antibiotics 61](#_Toc77598672)

[HEMODYNAMIC MANAGEMENT 62](#_Toc77598673)

[Fluid management 62](#_Toc77598674)

[Vasopressors 65](#_Toc77598675)

[Inotropes 69](#_Toc77598676)

[Monitoring and intravenous access 70](#_Toc77598677)

[Fluid balance 73](#_Toc77598678)

[VENTILATION 74](#_Toc77598679)

[Oxygen targets 74](#_Toc77598680)

[High-flow nasal oxygen therapy 75](#_Toc77598681)

[Non-invasive ventilation 76](#_Toc77598682)

[Protective ventilation in acute respiratory distress syndrome (ARDS) 77](#_Toc77598683)

[Low tidal volume in non-ARDS Respiratory Failure 80](#_Toc77598684)

[Recruitment Manoeuvres 80](#_Toc77598685)

[Prone Ventilation 81](#_Toc77598686)

[Neuromuscular blocking agents 82](#_Toc77598687)

[Extracorporeal membrane oxygenation (ECMO) 83](#_Toc77598688)

[ADDITIONAL THERAPIES 84](#_Toc77598689)

[Corticosteroids 84](#_Toc77598690)

[Blood Purification 85](#_Toc77598691)

[Red Blood Cell (RBC) Transfusion Targets 86](#_Toc77598692)

[Immunoglobulins 87](#_Toc77598693)

[Stress Ulcer Prophylaxis 88](#_Toc77598694)

[Venous Thromboembolism (VTE) Prophylaxis 89](#_Toc77598695)

[Renal Replacement therapy 90](#_Toc77598696)

[Glucose control 91](#_Toc77598697)

[Vitamin C 93](#_Toc77598698)

[Bicarbonate Therapy 94](#_Toc77598699)

[Nutrition 95](#_Toc77598700)

[LONG-TERM OUTCOMES AND GOALS OF CARE 96](#_Toc77598701)

[Goals of Care 96](#_Toc77598702)

[Palliative Care 98](#_Toc77598703)

[Peer support groups 100](#_Toc77598704)

[Transitions of care 101](#_Toc77598705)

[Screening for economic or social support 102](#_Toc77598706)

[Sepsis education for patients and families 103](#_Toc77598707)

[Shared decision making 103](#_Toc77598708)

[Discharge planning 104](#_Toc77598709)

[Cognitive therapy 107](#_Toc77598710)

[Post discharge follow up 108](#_Toc77598711)

[BIBLIOGRAPHY 110](#_Toc77598712)

# Legend of tables

[Table 1. Description of implications of strength of recommendation for patients, clinicians and policymakers. 16](#_Toc77598713)

[Table 2. Table of recommendations 19](#_Toc77598714)

[Table 3. Summary of changes since 2016. 28](#_Toc77598715)

[Table 4. Examples of risk factors for fungal infection. The decision to start empirical antifungal therapy depends on the type and number of risk factors, along with the locale epidemiology of fungal infections. 49](#_Toc77598716)

[Table 5. Guidance for PK/PD based dosing for specific drug classes. 54](#_Toc77598717)

[Table 6. Planned duration of empirical antimicrobial therapy in RCTs of shorter versus longer duration of therapy according to clinical syndrome. 60](#_Toc77598718)

# INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year and killing between one in three and one in six of those it affects (2-4). Early identification and appropriate management in the initial hours after the development of sepsis improves outcomes.

The recommendations in this document are intended to provide guidance for the clinician caring for adult patients with sepsis or septic shock in the hospital setting. Recommendations from these guidelines cannot replace the clinician’s decision-making capability when presented with a unique patient’s clinical variables. These guidelines are intended to reflect best practice.

# 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 s 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 1**. 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 1. 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 1]. 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 favor 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 favor 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.

Table 2. Table of recommendations

|  |  |
| --- | --- |
| Recommendations | Strength of Recommendation |
| 1. For hospitals and health systems, we recommend using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (strong recommendation, moderate quality of evidence) and standard operating procedures for treatment. | ***Strong*** |
| 1. We recommend against using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock. | ***Strong*** |
| 1. For adults suspected of having sepsis, we suggest measuring blood lactate. | ***Weak*** |
| 1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately. | ***Best Practice Statement*** |
| 1. For patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate. | ***Weak*** |
| 1. For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion. | ***Weak*** |
| 1. For adults with septic shock on vasopressors, we recommend an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets. | ***Strong*** |
| 1. For adults with sepsis or septic shock who require ICU admission, we suggest admitting the patients to the ICU within 6 hours. | ***Weak*** |
| 1. For adults with suspected sepsis or septic shock but unconfirmed infection, we recommend continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected. | ***Best Practice statement*** |
| 1. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within one hour of recognition. | ***Strong*** |
| 1. For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness. | ***Best Practice Statement*** |
| 1. For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized. | ***Weak*** |
| 1. For adults with a low likelihood of sepsis without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient. | ***Weak*** |
| 1. For adults with suspected sepsis or septic shock, we suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone. | ***Weak*** |
| 1. For adults with sepsis or septic shock at high risk of MRSA, we recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage. | ***Best practice Statement*** |
| 1. For adults with sepsis or septic shock at low risk of MRSA, we suggest against using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage. | ***Weak*** |
| 1. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent. | ***Weak*** |
| 1. For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we suggest against using double gram-negative coverage once the causative pathogen and the susceptibilities are known | ***Weak*** |
| 1. For adults with sepsis or septic shock at high risk of fungal infection, we suggest using empiric antifungal therapy over no antifungal therapy | ***Weak*** |
| 1. For adults with sepsis or septic shock at low risk of fungal infection, we suggest against empiric use of antifungal therapy | ***Weak*** |
| 1. We make no recommendation on the use of antiviral agents. | ***No recommendation*** |
| 1. For adults with sepsis or septic shock, we suggest using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties. | ***Best practice Statement*** |
| 1. For adults with sepsis or septic shock, we recommend rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical. | ***Best practice Statement*** |
| 1. For adults with sepsis or septic shock, we recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established. | ***Best practice Statement*** |
| 1. For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation*.* | ***Weak*** |
| 1. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest using shorter over longer duration of antimicrobial therapy. | ***Weak*** |
| 1. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation. | ***Strong*** |
| 1. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend against using starches for resuscitation. | ***Strong*** |
| 1. For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation. | ***Weak*** |
| 1. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors. | ***Strong*** |
| 1. For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine. | ***Weak*** |
| 1. For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine. | ***Weak*** |
| 1. For adults with septic shock, we suggest against using terlipressin. | ***Weak*** |
| 1. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone. | ***Weak*** |
| 1. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest against using levosimendan. | ***Weak*** |
| 1. For adults with septic shock, we suggest invasive monitoring of arterial blood pressure over non-invasive monitoring, as soon as practical and if resources are available. | ***Weak*** |
| 1. For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured. | ***Weak*** |
| 1. There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation. | ***No recommendation*** |
| 1. There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure. | ***No recommendation*** |
| 1. For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over non-invasive ventilation. | ***Weak*** |
| 1. There is insufficient evidence to make a recommendation on the use of non-invasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure. | ***No recommendation*** |
| 1. For adults with sepsis-induced ARDS, we recommend using a low tidal volume ventilation strategy (6 mL/kg), over a high tidal volume strategy (>10 mL/kg). | ***Strong*** |
| 1. For adults with sepsis-induced severe ARDS, we recommend using an upper limit goal for plateau pressures of 30 cm H2O, over higher plateau pressures | ***Strong*** |
| 1. For adults with moderate to severe sepsis-induced ARDS, we suggest using higher PEEP over lower PEEP. | ***Weak*** |
| 1. For adults with sepsis-induced respiratory failure (without ARDS), we suggest using low tidal volume as compared to high tidal volume ventilation. | ***Weak*** |
| 1. For adults with sepsis-induced moderate-severe ARDS, we suggest using traditional recruitment maneuvers. | ***Weak*** |
| 1. When using recruitment maneuvers, we recommend against using incremental PEEP titration/strategy. | ***Strong*** |
| 1. For adults with sepsis-induced moderate-severe ARDS, we recommend using prone ventilation for greater than 12 hours daily. | ***Strong*** |
| 1. For adults with sepsis induced moderate-severe ARDS, we suggest using intermittent NMBA boluses, over NMBA continuous infusion. | ***Weak*** |
| 1. For adults with sepsis-induced severe ARDS, we suggest using Veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use. | ***Weak*** |
| 1. For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids. | ***Weak*** |
| 1. For adults with sepsis or septic shock we suggest against using polymyxin B hemoperfusion. | ***Weak*** |
| 1. There is insufficient evidence to make a recommendation on the use of other blood purification techniques. | ***No recommendation*** |
| 1. For adults with sepsis or septic shock we recommend using a restrictive (over liberal) transfusion strategy. | ***Strong*** |
| 1. For adults with sepsis or septic shock we suggest against using intravenous immunoglobulins | ***Weak*** |
| 1. For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we suggest using stress ulcer prophylaxis. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication to such therapy exists. | ***Strong*** |
| 1. For adults with sepsis or septic shock, we recommend using low molecular weight heparin over unfractionated heparin for VTE prophylaxis | ***Strong*** |
| 1. For adults with sepsis or septic shock, we suggest against using mechanical VTE prophylaxis, in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone. | ***Weak*** |
| 1. In adults with sepsis or septic shock and AKI, we suggest using either continuous or intermittent renal replacement therapy. | ***Weak*** |
| 1. In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we suggest against using renal replacement therapy. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend initiating insulin therapy at a glucose level of ≥ 180mg/dL (10mmol/L). | ***Strong*** |
| 1. For adults with sepsis or septic shock we suggest against using IV vitamin C. | ***Weak*** |
| 1. For adults with septic shock and hypoperfusion-induced lactic acidemia, we suggest against using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements. | ***Weak*** |
| 1. For adults with septic shock and severe metabolic acidemia (pH ≤ 7.2) and acute kidney injury (AKIN score 2 or 3), we suggest using sodium bicarbonate therapy | ***Weak*** |
| 1. For adult patients with sepsis or septic shock who can be fed enterally, we suggest early (within 72 hours) initiation of enteral nutrition. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we recommend discussing goals of care and prognosis with patients and families over no such discussion. | ***Best Practice Statement*** |
| 1. For adults with sepsis or septic shock, we suggest addressing goals of care early (within 72 hours) over late (72 hours or later). | ***Weak*** |
| 1. For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation on any specific standardized criterion to trigger goals of care discussion. | ***No recommendation*** |
| 1. For adults with sepsis or septic shock, we recommend that the principles of palliative care (which may include palliative care consultation based on clinician judgement) be integrated into the treatment plan, when appropriate, to address patient and family symptoms and suffering. | ***Best Practice Statement*** |
| 1. For adults with sepsis or septic shock, we suggest against routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgement. | ***Weak*** |
| 1. For adult survivors of sepsis or septic shock and their families, we suggest referral to peer support groups over no such referral. | ***Weak*** |
| 1. For adults with sepsis or septic shock, we suggest using a handoff process of critically important information at transitions of care over no such handoff process. | ***Weak*** |
| 1. For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation on the use of any specific structured handoff tool over usual handoff processes. | ***No recommendation*** |
| 1. For adults with sepsis or septic shock and their families, we recommend screening for economic and social support (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs. | ***Best Practice Statement*** |
| 1. For adults with sepsis or septic shock and their families, we suggest offering written and verbal sepsis education (diagnosis, treatment, and post-ICU/post-sepsis syndrome) prior to hospital discharge and in the follow-up setting. | ***Weak*** |
| 1. For adults with sepsis or septic shock and their families, we recommend the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible. | ***Best Practice Statement*** |
| 1. For adults with sepsis and septic shock and their families, we suggest using a critical care transition program, compared to usual care, upon transfer to the floor. | ***Weak*** |
| 1. For adults with sepsis and septic shock, we recommend reconciling medications at both ICU and hospital discharge. | ***Best Practice Statement*** |
| 1. For adult survivors of sepsis and septic shock and their families, we recommend including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary. | ***Best Practice Statement*** |
| 1. For adults with sepsis or septic shock who developed new impairments, we recommend hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae. | ***Best Practice Statement*** |
| 1. For adults with sepsis or septic shock and their families, there is insufficient evidence to make a recommendation on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up. | ***No recommendation*** |
| 1. For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation for or against early cognitive therapy. | ***No recommendation*** |
| 1. For adult survivors of sepsis or septic shock, we recommend assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge. | ***Best Practice Statement*** |
| 1. For adult survivors of sepsis or septic shock, we suggest referral to a post-critical illness follow-up program if available. | ***Weak*** |
| 1. For adult survivors of sepsis or septic shock receiving mechanical ventilation for >48hours or an ICU stay of >72 hours, we suggest referral to a post-hospital rehabilitation program. | ***Weak*** |

Table 3. Summary of changes since 2016.

**Arrow up implies strengthening of recommendation and arrow down weakening.**

|  |  |
| --- | --- |
| **INITIAL RESUSCITATION** | |
| **2016 Guidelines** | |
| * **We recommend that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours** (Strong recommendation, low quality of evidence) |  |
| **2021 Guidelines** | |
| * **For patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation** (Weak recommendation, low quality evidence) | Arrow: Rotate right with solid fill |
| * **For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.** (Weak recommendation, low quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **SCREENING FOR SEPSIS** | |
| **2016 Guidelines** | |
| * **We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high risk patients.** (Best Practice Statement) |  |
| **2021 Guidelines** | |
| * **For hospitals and health systems, we recommend using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients** (strong recommendation, moderate quality of evidence) **and standard operating procedures for treatment.** | Arrow: Anti-clockwise curve with solid fill |
| * **We recommend against using qSOFA compared to SIRS, NEWS, or MEWS as a screening tool for sepsis or septic shock.** (Strong recommendation, moderate quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **TIMING OF ANTIMICROBIAL THERAPY** | |
| **2016 Guidelines** | |
| * **We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock** (strong recommendation; moderate quality of evidence). |  |
| **2021 Guidelines** | |
| * **For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within one hour of recognition.**Strong recommendation low quality of evidence (Septic shock). Strong recommendation very low quality of evidence (Sepsis without shock) | **NEW** |
| * **For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized.** (Weak recommendation, very low quality of evidence) | **NEW** |
| * **For adults with a low likelihood of sepsis without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient.** (Weak recommendation, very low quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **ANTIMICROBIAL THERAPY** | |
| **2016 Guidelines** | |
| * **We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage**. (Strong recommendation; moderate quality of evidence) |  |
| **2021 Guidelines** | |
| * **For adults with sepsis or septic shock at high risk of MRSA, we recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage.** Best practice statement. | **NEW** |
| * **For adults with sepsis or septic shock at low risk of MRSA, we suggest against using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage.** (Weak recommendation, low quality of evidence) | **NEW** |
| * **For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative cover for empiric treatment over one gram-negative agent.** (Weak recommendation, very low quality of evidence) | **NEW** |
| * **For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.** (Weak recommendation, very low quality of evidence) | **NEW** |
| * **For adults with sepsis or septic shock at high risk of fungal infection, we suggest using empiric antifungal therapy over no antifungal therapy** (Weak recommendation, low quality of evidence) | **NEW** |
| * **For adults with sepsis or septic shock at low risk of fungal infection, we suggest against empiric use of antifungal therapy.** (Weak recommendation, low quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **HAEMODYNAMIC SUPPORT** | |
| **2016 Guidelines** | |
| * **We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock** (Weak recommendation, low quality of evidence |  |
| * **We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock.** (Weak recommendation, low quality evidence). |  |
| **2021 Guidelines** | |
| * **There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.** (No recommendation) | **NEW** |
| * **For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.** (Weak recommendation, low quality of evidence) | Arrow: Anti-clockwise curve with solid fill |
| * **For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation.** (Weak recommendation, moderate quality of evidence) | Arrow: Anti-clockwise curve with solid fill |

|  |  |
| --- | --- |
| **MONITORING AND SUPPORT** | |
| **2021 Guidelines** | |
| * **For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.** (Weak recommendation, very low quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **INOTROPIC SUPPORT** | |
| **2021 Guidelines** | |
| * **For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest against using levosimendan**.(Weak recommendation, low quality of evidence) | **NEW** |

|  |  |
| --- | --- |
| **CORTICOSTEROIDS** | |
| **2016 Guidelines** | |
| * **We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day.** (Weak recommendation; low quality of evidence) |  |
| **2021 Guidelines** | |
| * **For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids.** (Weak recommendation, moderate quality of evidence). | Arrow: Anti-clockwise curve with solid fill |

|  |  |
| --- | --- |
| **BLOOD PURIFICATION** | |
| **2016 Guidelines** | |
| * **We make no recommendation regarding the use of blood purification techniques** |  |
| **2021 Guidelines** | |
| * **For adults with sepsis or septic shock we suggest against using polymyxin B haemoperfusion.** (Weak recommendation, low quality of evidence). | Arrow: Anti-clockwise curve with solid fill |

|  |  |
| --- | --- |
| **RESPIRATORY SUPPORT** | |
| **2021 Guidelines** | |
| * **For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over non-invasive ventilation.** (Weak recommendation, low quality of evidence). | **NEW** |
| * **For adults with sepsis-induced severe ARDS, we suggest using Veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use.** Weak recommendation, low quality of evidence). | **NEW** |

|  |  |
| --- | --- |
| **VITAMIN C** | |
| **2021 Guidelines** | |
| * **For adults with sepsis or septic shock we suggest against using IV vitamin C.** (Weak recommendation, low quality of evidence). | **NEW** |

# SCREENING AND EARLY TREATMENT

## Screening for patients with sepsis and septic shock

|  |
| --- |
| Recommendations |
| 1. For hospitals and health systems, we recommend using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment.   *Strong recommendation, moderate quality of evidence for screening.*  *Strong recommendation, very low-quality evidence for standard operating procedures.* |

**Rationale:**

Sepsis performance improvement programs generally consist of sepsis screening, education, measurement of sepsis bundle performance, patient outcomes, and actions for identified opportunities (25, 26). Despite some inconsistency, a meta-analysis of 50 observational studies on the effect of performance improvement programs showed that these programs were associated with better adherence to sepsis bundles along with a reduction in mortality (OR 0.66; 95% CI, 0.61–0.72) in patients with sepsis and septic shock (27). The specific components of performance improvement did not appear to be as important as the presence of a program that included sepsis screening and metrics.

Sepsis screening tools are designed to promote early identification of sepsis and consist of manual methods or automated use of the electronic health record (EHR). There is wide variation in diagnostic accuracy of these tools with most having poor predictive values, although the use of some was associated with improvements in care processes (28-31). A variety of clinical variables and tools are used for sepsis screening, such as systemic inflammatory response syndrome (SIRS) criteria, vital signs, signs of infection, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) (26, 32). Machine learning may improve performance of screening tools, and in a meta-analysis of 42,623 patients from seven studies for predicting hospital acquired sepsis the pooled area under the receiving operating curve (SAUROC) (0.89; 95% CI 0.86-0.92); sensitivity (81%; 95% CI 80-81), and specificity (72%; 95% CI 72-72) was higher for machine learning than the SAUROC for traditional screening tools such as SIRS (0.70), MEWS (0.50), and SOFA (0.78) (32).

Screening tools may target patients in various locations, such as in-patient wards, emergency departments, or intensive care units (ICU).(28-30, 32) A pooled analysis of 3 RCTs did not demonstrate a mortality benefit of active screening (RR 0.90; 95% CI, 0.51-1.58) (33-35). However, while there is wide variation in sensitivity and specificity of sepsis screening tools, they are an important component of identifying sepsis early for timely intervention.

Standard operating procedures are a set of practices that specify a preferred response to specific clinical circumstances (36). Sepsis standard operating procedures, initially specified as Early Goal Directed Therapy have evolved to “usual care” which includes a standard approach with components of the sepsis bundle, early identification, lactate, cultures, antibiotics, and fluids (37). A large study examined the association between implementation of state-mandated sepsis protocols, compliance, and mortality. A retrospective cohort study of 1,012,410 sepsis admissions to 509 hospitals in the United States in a retrospective cohort examined mortality before (27 months) and after (30 months) implementation of New York state sepsis regulations, with a concurrent control population from 4 other states (38). In this comparative interrupted time series, mortality was lower in hospitals with higher compliance with achieving the sepsis bundles successfully.

Lower resource countries may experience a different effect. A meta-analysis of 2 RCTs in Sub-Saharan Africa found higher mortality (RR 1.26; 95% CI 1.00-1.58) with standard operating procedures compared with usual care, while it was decreased in one observational study (adjusted hazard ratio [HR]; 95% CI, 0.55-0.98) (39).

|  |
| --- |
| Recommendations |
| 1. We recommend against using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.   *Strong recommendation, moderate-quality evidence.* |

**Rationale**

The qSOFA uses 3 variables to predict death and prolonged ICU stay in patients with known or suspected sepsis: a Glasgow Coma Score < 15, a respiratory rate ≥22 breaths/min and a systolic blood pressure ≤100 mmHg. When any two of these variables are present simultaneously the patient is considered to be qSOFA positive. Data analysis used to support the recommendations of the 3rd International Consensus Conference on the Definitions of Sepsis identified qSOFA as a predictor of poor outcome in patients with known or suspected infection, but no analysis was performed to support its use as a screening tool (5). Since that time numerous studies have investigated the potential use of the qSOFA as a screening tool for sepsis (40-42). The results have been contradictory as to its usefulness. Studies have shown that qSOFA is more specific but less sensitive than having 2 of 4 SIRS criteria for early identification of infection induced organ dysfunction (40-43). Neither SIRS nor qSOFA are ideal screening tools for sepsis and the bedside clinician needs to understand the limitations of each. In the original derivation study, authors found that only 24% of infected patients had a qSOFA score 2 or 3, but these patients accounted for 70% of poor outcomes (5). Similar findings have also been found when comparing against the National Early warning Score (NEWS) and the Modified Early warning Score (MEWS) (44). Although the presence of a positive qSOFA should alert the clinician to the possibility of sepsis in all resource settings; given the poor sensitivity of the qSOFA, the panel issued a strong recommendation against its use as a single screening tool.

|  |
| --- |
| Recommendations |
| 1. For adults suspected of having sepsis, we suggest measuring blood lactate.   *Weak recommendation, low-quality evidence.* |

**Rationale**

The association of lactate level with mortality in patients with suspected infection and sepsis is well established (45, 46). Its use is currently recommended as part of the SSC Hour-1 sepsis bundle for those patients with sepsis (47, 48), and an elevated lactate is part of the Sepsis-3 definition of septic shock (49). It has been suggested that lactate can also be used to screen for the presence of sepsis among undifferentiated adult patients with clinically suspected (but not confirmed) sepsis. Several studies have assessed the use of lactate in this context (50-52).

The lactate cutoffs determining an elevated level ranged from 1.6-2.5 mmol/L, though diagnostic characteristics were similar regardless of the cutoff. Sensitivities range from 66-83%, with specificities ranging from 80-85%. Pooled positive and negative likelihood ratios from the three studies are 4.75 and 0.29, respectively. Studies showed an association between the use of point-of-care lactate measurements at presentation and reduced mortality; however, the results are inconsistent (53). In summary, the presence of an elevated or normal lactate level significantly increases or decreases, respectively, the likelihood of a final diagnosis of sepsis in patients with suspected sepsis. However, lactate alone is neither sensitive nor specific enough to rule-in or rule-out the diagnosis on its own. Lactate testing may not be readily available in many resource-limited settings (54-61). Therefore, we issued a weak recommendation favoring the use of serum lactate as an adjunctive test to modify the pre-test probability of sepsis in patients with suspected but not confirmed sepsis.

## Initial Resuscitation

|  |
| --- |
| Recommendations |
| 1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately.   *Best Practice Statement.* |
| 1. For patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation.   *Weak recommendation, low quality evidence.* |
| 1. For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination or static parameters alone.   *Weak recommendation, very low-quality evidence.*  Remarks:  Dynamic parameters include response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, where available |
| 1. For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.   *Weak recommendation, low quality evidence*  Remarks  During acute resuscitation, serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate. |
| 1. For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.   *Weak recommendation, low quality evidence.* |

***Rationale***

Timely, effective fluid resuscitation is crucial for the stabilization of sepsis-induced tissue hypoperfusion in sepsis and septic shock. Previous guidelines recommend initiating appropriate resuscitation immediately upon recognition of sepsis or septic shock and having a low threshold for commencing it in those patients where sepsis is not proven but is suspected. Although the evidence stems from observational studies, this recommendation is considered a best practice and there are no new data suggesting that a change is needed.

The 2016 SSC guideline issued a recommendation for using a minimum of 30ml/kg (ideal body weight) of IV crystalloids in initial fluid resuscitation. This fixed volume of initial resuscitation was based on observational evidence (62). There are no prospective intervention studies comparing different volumes for initial resuscitation in sepsis or septic shock. A retrospective analysis of adults presenting to an emergency department with sepsis or septic shock showed that failure to receive 30ml/kg of crystalloid fluid therapy within 3 hours of sepsis onset was associated with increased odds of in-hospital mortality, delayed resolution of hypotension and increased length of stay in ICU, irrespective of comorbidities, including end-stage kidney disease and heart failure (63). In the PROCESS (64), ARISE (65) and PROMISE (66) trials, the average volume of fluid received pre-randomization was also in the range of 30ml/kg, suggesting that this fluid volume has been adopted in routine clinical practice (67).

Most patients require continued fluid administration following initial resuscitation. Such administration needs to be balanced with the risk of fluid accumulation and potential harm associated with fluid overload, in particular, prolonged ventilation, progression of acute kidney injury (AKI) and increased mortality. One of the most important principles of managing complex septic patients is the need for a detailed initial assessment and ongoing re-evaluation of the response to treatment. To avoid over- and under- resuscitation, fluid administration beyond the initial resuscitation should be guided by careful assessment of intravascular volume status and organ perfusion. Heart rate, central venous pressure (CVP) and systolic blood pressure alone are poor indicators of fluid status. Dynamic measures have demonstrated better diagnostic accuracy at predicting fluid responsiveness compared with static techniques. Dynamic measures include passive leg raising combined with cardiac output (CO) measurement, fluid challenges against stroke volume (SV), systolic pressure or pulse pressure, and increases of SV in response to changes in intrathoracic pressure. In a systematic review and meta-analysis, dynamic assessment to guide fluid therapy was associated with reduced mortality (RR 0.59; 95% CI 0.42 to 0.83), ICU length of stay (MD –1.16 days; 95% CI –1.97 to –0.36), and duration of mechanical ventilation (-2.98 hours; 95% CI -5.08 to -0.89) (3). However, in one other meta-analysis, there was no significant difference in mortality between septic patients resuscitated with a volume responsiveness-guided approach compared with standard resuscitative strategies (68). Most data arise from high income settings and a paucity of evidence exists in resource-limited settings to guide optimal titration of fluid resuscitation as well as the appropriate safety end- points. An RCT in patients with sepsis and hypotension in Zambia showed that early protocolized resuscitation with administration of IV fluids guided by jugular venous pressure, respiratory rate, and arterial oxygen saturation only, was associated with significantly more fluid administration in the first 6 hours [median 3.5L (IQR 2.7-4.0) versus 2.0L (IQR 1.0 – 2.5)] and higher hospital mortality (48.1% versus 33%) than standard care (69).

If fluid therapy beyond the initial 30ml/kg administration is required, clinicians may use repeated small boluses guided by objective measures of SV and/or CO. In post-cardiac surgery patients, fluid challenges of 4ml/kg compared to 1 to 3ml/kg increased the sensitivity of detecting fluid responders and non-responders based on measurement of CO (70). In resource-limited regions where measurement of CO or SV may not be possible, a > 15% increase in pulse pressure could indicate that the patient is fluid responsive utilizing a passive leg-raise test for 60-90 seconds (71, 72).

Serum lactate is an important biomarker of tissue hypoxia and dysfunction, but is not a direct measure of tissue perfusion (73). Recent definitions of septic shock include increases in lactate as evidence of cellular stress to accompany refractory hypotension (1). Previous iterations of these guidelines have suggested using lactate levels as a target of resuscitation in the early phases of sepsis and septic shock, based on earlier studies related to goal-directed therapy and meta-analyses of multiple studies targeting reductions in serum lactate in comparison to “standard care” or increases in central venous oxygen saturation (74, 75). The panel recognizes that normal serum lactate levels are not achievable in all patients with septic shock, but these studies support resuscitative strategies that decrease lactate toward normal. Serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate. As with sepsis screening, lactate measurement may not always be available in some resource-limited settings.

When advanced hemodynamic monitoring is not available, alternative measures of organ perfusion may be used to evaluate the effectiveness and safety of volume administration. Temperature of the extremities, skin mottling and capillary refill time (CRT) have been validated and shown to be reproducible signs of tissue perfusion (76, 77). The ANDROMEDA-SHOCK study evaluated whether a resuscitation strategy targeting CRT normalization was more effective than a resuscitation strategy aiming at normalization or decreasing lactate levels by 20% every 2 hours in the first 8 hours of septic shock (58). At day 3, the CRT group had significantly less organ dysfunction as assessed by SOFA score [mean SOFA score 5.6 (SD 4.3) versus 6.6 (SD 4.7); p=0.045]. 28-day mortality was 34.9% in the peripheral perfusion group and 43.4% in the lactate group, but this difference did not reach statistical significance (HR 0.75; 95% CI 0.55–1.02). Despite the absence of a clear effect on mortality, using CRT during resuscitation has physiologic plausibility and is easily performed, non-invasive, and no cost. However, this approach should be augmented by careful, frequent, and comprehensive patient evaluation to predict or recognize fluid overload early, particularly where critical care resources are constrained. Relevant consideration of the background pathology or pathological processes pertinent to the patient should also inform management (69, 78).

## Mean Arterial Pressure

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock on vasopressors, we recommend an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets   *Strong recommendation, moderate-quality evidence.* |

**Rationale**

MAP is a key determinant of mean systemic filling pressure, which in turn, is the major driver of venous return and CO. Increasing MAP therefore usually results in increased tissue blood flow and augments the supply side of tissue perfusion. While some tissues, such as the brain and kidneys have the ability to auto-regulate blood flow, MAPs below a threshold, usually understood to be approximately 60 mm Hg, are associated with decreased organ perfusion, which tracks linearly with MAP (79). Previous SSC guidelines recommended targeting a MAP of greater than 65 mm Hg for initial resuscitation. The recommendation was based principally on a RCT in septic shock comparing patients who were given vasopressors to target a MAP of 65 - 70 mm Hg, versus a target of 80 - 85 mm Hg (80). This study found no difference in mortality, although a sub-group analysis demonstrated a 10.5% absolute reduction in renal replacement therapy (RRT) with higher MAP targets among patients with chronic hypertension. Additionally, targeting higher MAP with vasopressors was associated with a higher risk of atrial fibrillation. A limitation of this study was that the average MAP in both arms exceeded the targeted range. A meta-analysis of two RCTs on this topic supported that higher MAP targets did not improve survival in septic shock (RR 1.05; 95% CI 0.90 - 1.23) (81).

A recent RCT, monitored to ensure protocol and MAP target compliance, compared a “permissive hypotension” (MAP 60 – 65 mm Hg) group with a “usual care” group that received vasopressors and MAP targets set by the treating physician in patients aged 65 years and older with septic shock (82, 83). The intervention group in this study achieved a mean MAP of 66.7 mm Hg, compared with 72.6 mm Hg in the usual care group. Among 2463 analyzed patients, there was significantly less exposure to vasopressors in the intervention group, measured by duration of vasopressor infusion and total vasopressor doses expressed in norepinephrine equivalents. Ninety-day mortality in the permissive hypotension and usual care groups was similar (41.0% vs 43.8%).

Given the lack of advantage associated with higher MAP targets and the lack of harm among elderly patients with MAP targets of 60 – 65 mm Hg, the panel recommends targeting a MAP of 65 mm Hg in the initial resuscitation of patients with septic shock who require vasopressors.

## Admission to Intensive Care

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock who require ICU admission, we suggest admitting the patients to the ICU within 6 hours.   *Weak recommendation, low-quality evidence.* |

***Rationale***

The outcome of critically ill patients depends on timely application of critical care interventions in an appropriate environment. Outside the ICU, septic patients are typically seen in the emergency department (ED) and hospital wards. Delayed admissions of critically ill patients from ED are associated with decreased sepsis bundle compliance and increased mortality, ventilator duration, and ICU and hospital length of stay (84). Data on the optimal time for transfer to the ICU stem from observational studies and registry databases.

In an observational study of 401 ICU patients, authors reported an increase in ICU mortality of 1.5% for each hour delay of ED to ICU transfer (85). A retrospective observational study of 14788 critically ill patients in the Netherlands showed a higher hospital mortality for the higher ED to ICU time quintiles (2.4–3.7hr and > 3.7hr) compared with the lowest ED to ICU time quintile (< 1.2hr) (86). When adjusted for severity of illness, an ED to ICU time > 2.4hr was associated with increased hospital mortality in patients with higher illness severity (ORs of 1.20 (95% CI, 1.03–1.39). Patients with sepsis were not studied separately.

Another study evaluated 50,322 ED patients admitted to 120 US ICUs (87). Mortality increased when ED stay exceeded 6 hours (17% vs 12.9%, p<0.001). Among hospital survivors, the delayed admission group had a longer hospital stay, higher mortality, and higher rates of mechanical ventilation and central venous catherization. Similarly, another study of 12,380 ward patients in 48 UK hospitals showed that (88) delayed admission to ICU led to higher 90-day mortality and further physiological deterioration.

Based on existing data, timely admission of critically ill patients to an ICU environment may result in better patient outcomes. There is also evidence of improved patient satisfaction, increased patient safety, better patient flow and improved staff morale (89). However, although critical care services are likely best delivered in an ICU environment, there are multiple reasons why immediate transfer of critically ill patients with sepsis to an ICU may not always be possible, in particular in lower and middles income countries (LMIC), where ICU bed availably can be limited. In this case, regular assessment, evaluation, and appropriate treatment should not be delayed, independent of patient location.

# INFECTION

## Diagnosis of infection

|  |
| --- |
| Recommendations |
| 1. For adults with suspected sepsis or septic shock but unconfirmed infection, we recommend continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.   *Best Practice statement.* |

**Rationale**

In previous versions of these guidelines, we highlighted the importance of obtaining a full screen for infectious agents prior to starting antimicrobials wherever it is possible to do so in a timely fashion. (12, 13) As a best practice statement, we recommended that appropriate routine microbiologic cultures (including blood) should be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if it results in no substantial delay in the start of antimicrobials (i.e., < 45 minutes). This recommendation has not been updated in this version but remains as valid as before.

The signs and symptoms of sepsis are nonspecific and often mimic multiple other diseases (90-92). Since there is no “gold standard” test to diagnose sepsis, the bedside provider cannot have a differential diagnosis of sepsis alone in a patient with organ dysfunction. Indeed, a third or more of patients initially diagnosed with sepsis turn out to have non-infectious conditions (90, 93, 94). Best practice is to continually assess the patient to determine if other diagnoses are more or less likely, especially since a patient’s clinical trajectory can evolve significantly after hospital admission, increasing or decreasing the likelihood of a diagnosis of sepsis. With this uncertainty, there can be significant challenges in determining when it is “appropriate” to de-escalate or discontinue antibiotics.

Another major challenge is implementing a system that reminds clinicians to focus on the fact that the patient is still receiving antibiotics each day, especially as providers rotate in and out of the care team. Systems that promote such reassessment by automatic stop orders, electronic prompts, or mandatory check lists all seem useful in theory, but each has disadvantages in terms of provider acceptance or assuring that providers thoughtfully assess the need for antibiotics rather than checking a box in the electronic record or reflexively acknowledging a prompt, without considering its underlying rationale (95).

We did not identify any direct or indirect evidence assessing this important issue. Thus, clinicians are strongly encouraged to discontinue antimicrobials if a non-infectious syndrome (or an infectious syndrome that does not benefit from antimicrobials) is demonstrated or strongly suspected. Since this situation is not always apparent, continued reassessment of the patient should optimize the chances of infected patients receiving antimicrobial therapy and non-infected patients avoiding therapy that is not indicated.

## Time to antibiotics

|  |
| --- |
| Recommendations |
| 1. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within one hour of recognition.   *Strong recommendation low quality of evidence (Septic shock)*  *Strong recommendation very low quality of evidence (Sepsis without shock)* |
| 1. For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.   *Best Practice Statement*  Remarks  Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient’s presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high. |
| 1. For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized.   *Weak recommendation, very low quality of evidence.* |
| 1. For adults with a low likelihood of sepsis without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient.   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Early administration of appropriate antimicrobials is one of the most effective interventions to reduce mortality in patients with sepsis (96-98). Delivering antimicrobials to patients with sepsis or septic shock should therefore be treated as an emergency. The imperative to provide antimicrobials as early as possible, however, must be balanced against the potential harms associated with administering unnecessary antimicrobials to patients without infection (99, 100). These include a range of adverse events such as allergic or hypersensitivity reactions, kidney injury, thrombocytopenia, *Clostridoides difficile* infection, and antimicrobial resistance (101-106). Accurately diagnosing sepsis is challenging as sepsis can present in subtle ways, and some presentations that first appear to be sepsis turn out to be non-infectious conditions (90, 93, 107, 108). Evaluating the likelihood of infection and severity-of-illness for each patient with suspected sepsis should inform the necessity and urgency of antimicrobials (99, 100).

The mortality reduction associated with early antimicrobials appears strongest in patients with septic shock, where a number of studies have reported a strong association between time-to- antibiotics and death in patients with septic shock but weaker associations in patients without septic shock (98, 109, 110). In a study of 49,331 patients treated at 149 New York hospitals, each additional hour of time from ED arrival to administration of antimicrobials was associated with 1.04 increased odds of in-hospital mortality, *p*<0.001 (1.07 (95%CI 1.05-1.09) for patients receiving vasopressors vs. 1.01 (95%CI 0.99-1.04) for patients not on vasopressors) (98). In a study of 35,000 patients treated at Kaiser Permanente Northern California, each additional hour of time from ER arrival to administration of antimicrobials was associated with 1.09 increased odds of in-hospital mortality (1.07 for patients with “severe” sepsis (lactate ≥2, at least one episode of hypotension, required non-invasive or invasive mechanical ventilation or has organ dysfunction) and 1.14 for patients with septic shock); which equated to a 0.4% absolute mortality increase for “severe” sepsis and a 1.8% absolute increase for septic shock (110). Finally, in a study of 10,811 patients treated in four Utah hospitals, each hour delay in time from ED arrival to administration of antimicrobials was associated with 1.16 increased odds of in-hospital and 1.10 increased odds of 1-year mortality (1.13 in patients with hypotension vs 1.09 in patients without hypotension) (111). Other studies, however, did not observe an association between antimicrobial timing and mortality (112-117) and more recently (112, 114). It should be noted that all the aforementioned studies were observational analyses and hence at risk of bias due to insufficient sample size, inadequate risk-adjustment, blending together the effects of large delays until antibiotics with short delays, or other study design issues (118).

In patients with sepsis without shock, the association between time to antimicrobials and mortality within the first few hours from presentation is less consistent (98, 110). Two RCTs have been published (119, 120). One failed to achieve a difference in time-to-antimicrobials between arms (120). The other found no significant difference in mortality despite a 90-minute difference in median time interval to antimicrobial administration (119). Observational studies do, however, suggest that mortality may increase after intervals exceeding 3-5 hours from hospital arrival and/or sepsis recognition (98, 111, 119, 120). We therefore suggest initiating antibiotics in patients with possible sepsis without shock as soon as sepsis appears to be the most likely diagnosis, and no later than 3 hours after sepsis was first suspected if concern for sepsis persists at that time.

Overall, given the high risk of death with septic shock and the strong association of antimicrobial timing and mortality, the panel issued a strong recommendation to administer antimicrobials immediately, and within one hour, in all patients with potential septic shock. Additionally, for patients with confirmed/very likely sepsis, we recommend antimicrobials be administered immediately (figure 1). For patients with possible sepsis without shock, we recommend a rapid assessment of infectious and non-infectious etiologies of illness be undertaken to determine, within 3 hours, whether antibiotics should be administered or whether antibiotics should be deferred while continuing to monitor the patient closely.

Limited data from resource-limited settings suggest that timely administration of antimicrobials in patients with sepsis and septic shock is beneficial and potentially feasible (121-126). Access and availability of a wide range of antimicrobials in such settings may however vary (54, 55, 57, 59, 61). The availability and turn-around time for laboratory testing, rapid infectious diagnostic, imaging, etc. varies widely by regions and settings. As such, the rapid assessment of infectious and non-infectious etiologies of illness will differ across settings, depending on what is feasible to achieve. Recent recommendations pertaining to the use of antimicrobials in patients with sepsis and septic shock in resource-limited settings are in line with the current recommendations (123).

## Biomarkers to start antibiotics

|  |
| --- |
| Recommendations |
| 1. For adults with suspected sepsis or septic shock, we suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Procalcitonin is undetectable in healthy states, but rises rapidly in response to pro-inflammatory stimuli, especially bacterial infections (127). In theory, procalcitonin levels in combination with clinical evaluation may facilitate the diagnosis of serious bacterial infections and prompt early initiation of antimicrobials. In a meta-analysis of 30 studies (3244 patients), procalcitonin had a pooled sensitivity of 77% and specificity of 79% for sepsis in critically ill patients (128).

We identified direct evidence from 3 RCTs that compared procalcitonin-guided protocols for antibiotic initiation vs usual care (129-131). A meta-analysis of the 3 trials (n=1,769 ICU patients) found no difference in short-term mortality (RR 0.99; 95% CI 0.86 to 1.15), length of ICU stays (MD 0.19 days; 95% CI -0.98 to 1.36) or length of hospitalization (MD 7.00 days; 95% CI -26.24 to 12.24). Long-term mortality, readmission rates and hospital-free days were not reported in any of the trials, and no relevant studies on the costs associated with use of procalcitonin were found. In general, knowledge about the undesirable effects was lacking, and the quality of evidence was very low. Published guidelines for the management of community acquired pneumonia recommend initiation of antimicrobials for patients with community acquired pneumonia regardless of procalcitonin level (132).

With no apparent benefit, unknown costs, and limited availability in some settings including low- and middle-income countries (LMICs), the panel issued a weak recommendation against using procalcitonin to guide antimicrobial initiation in addition to clinical evaluation.

## Antimicrobial choice

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock at high risk of methicillin resistant staph aureus (MRSA), we recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage.   *Best practice Statement* |
| 1. For adults with sepsis or septic shock at low risk of methicillin resistant staph aureus (MRSA), we suggest against using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage.   *Weak recommendation, low quality of evidence.* |

**Rationale**

The decision on whether to include an antibiotic active against MRSA in an empiric treatment regimen for sepsis and septic shock depends upon a) the likelihood that the patient’s infection is caused by MRSA, b) the risk of harm associated with withholding treatment for MRSA in a patient with MRSA, and c) the risk of harm associated with MRSA treatment in a patient without MRSA.

MRSA accounts for approximately 5% of culture-positive infections among critically ill patients (133), and may be decreasing according to some reports (134, 135). The incidence of MRSA varies, however, by region (ranging from ~2% in Western Europe to 10% in North America) and by patient-related characteristics (133, 136, 137). Patient-related risk factors for MRSA include prior history of MRSA infection or colonization, recent IV antibiotics, history of recurrent skin infections or chronic wounds, presence of invasive devices, hemodialysis, recent hospital admissions and severity of illness (136, 138-142).

Observational data on the impact of including MRSA coverage in empiric regimens vary. Some studies focus on patients with documented MRSA infections, while others evaluate the impact of MRSA coverage in undifferentiated patients. Among patients with documented MRSA infections, delays of >24-48 hours until antibiotic administration are associated with increased mortality in some studies (143-147), but not in others (148-154). Among undifferentiated patients with pneumonia or sepsis, broad-spectrum regimens including agents active against MRSA were associated with higher mortality, particularly among patients without MRSA (137, 151, 155, 156). The undesirable effects associated with unnecessary MRSA coverage are also supported by studies showing an association between early discontinuation of MRSA coverage and better outcomes in patients with negative nares or bronchoalveolar lavage (BAL) MRSA PCR (157-159).

Failure to cover for MRSA in a patient with MRSA may be harmful, but unnecessary MRSA coverage in a patient without MRSA may also be harmful. Data from RCTs, including the evaluation of nasal swab testing to withhold therapy for MRSA, are warranted, and studies on rapid diagnostic tools and clinical prediction rules for MRSA are needed.

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.   *Weak recommendation, very low quality of evidence.* |
| 1. For adults with sepsis or septic shock and low risk for MDR organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.   *Weak recommendation, very low quality of evidence.* |
| 1. For adults with sepsis or septic shock, we suggest against using double gram-negative coverage once the causative pathogen and the susceptibilities are known   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Considering the increasing frequency of MDR bacteria in many parts of the world and associations between delays in active therapy and worse outcomes, the initial use of multidrug therapy is often required to ensure the empiric regimen includes at least one effective agent that is active against the offending organism (12, 13). In the empiric phase - before causative agent(s) and susceptibilities are known, the optimal choice of antibiotic therapy depends on the local prevalence of resistant organisms, patient risk factors for resistant organisms, and the severity of illness. In the directed/targeted phase, once causative agent(s) and susceptibilities are known, sustained double gram-negative coverage is rarely necessary except for patients with highly resistant organisms.

This was borne out in a recent systematic review with meta-analysis of 10 RCTs, no differences in mortality or other patient-important outcomes between empiric mono- vs.combination antibiotic therapy in adult ICU patients with severe sepsis or septic shock were observed, also when taking disease severity into consideration (160). Results from the largest RCT included in the meta-analysis (a comparison of sustained courses of moxifloxacin and meropenem vs meropenem alone in a low endemic resistance setting) were consistent with the findings from the meta-analysis (161).

Recommendations about the use of more than one gram-negative agent for empiric treatment over one gram-negative agent are challenging given clinical heterogeneity, including patient characteristics, source of infection, causative agents, and antibiotic resistance patterns. Local information about the resistance patterns of the most common causative agents of sepsis is essential to choose the most appropriate empiric antibiotic therapy. For this reason, we refrained from proposing recommendations regarding double gram-negative coverage in patients with sepsis or septic shock overall, but instead recommend tailoring the use of double coverage based on patients’ risk of MDR pathogens. Factors to guide this decision include: proven infection or colonization with antibiotic-resistant organisms within the preceding year, local prevalence of antibiotic-resistant organisms, hospital-acquired/healthcare associated· (versus community- acquired infection), broad-spectrum antibiotic use within the preceding 90 days, concurrent use selective digestive decontamination (SDD), travel to a highly endemic country within the preceding 90 days (see https:/ /resistancemap.cddep.org/) and hospitalization abroad within the preceding 90 days (162-164). In the directed/targeted phase, once causative agent(s) and susceptibilities are known, sustained double gram-negative coverage is not necessary except possibly for patients with highly resistant organisms with no proven safe and efficacious therapeutic option.

The overall quality of evidence was very low, and the direct costs of antibiotics can increase with the routine use of multiple agents for treatment. This may specifically have an impact in resource-limited settings.

In general, in patients at high risk for MDR organisms, we suggest using two gram negative agents for empiric treatment to increase the likelihood of adequate coverage, while in patients with a low risk for MDR organisms, we suggest using a single agents for empiric treatment, as there are no apparent benefits of using two agents and the a risk of antimicrobial-associated undesirable effects, including direct toxicity, *Clostridoides difficile* infection and development of antibiotic resistance (165). Empiric double coverage of gram-negative bacilli is most important in patients at high risk for resistant organisms with severe illness, particularly septic shock.

## Antifungal therapy

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock at high risk of fungal infection, we suggest using empiric antifungal therapy over no antifungal therapy   *Weak recommendation, low quality of evidence.* |
| 1. For adults with sepsis or septic shock at low risk of fungal infection, we suggest against empiric use of antifungal therapy   *Weak recommendation, low quality of evidence.* |

**Rationale**

Sepsis and septic shock due to fungi are most commonly observed in ICUs and are associated with poor outcomes (166-170). Some observational studies suggested that prompt initiation of appropriate empiric antifungal therapy may be associated with a reduction in mortality, however these studies do not prove a causal relationship between antifungal therapy and outcome, nor do they clarify the role of timing of treatment, and some other studies have failed to show this association (167, 171-173).

In an updated meta-analysis of empiric antifungal therapy versus no antifungal therapy in adult critically ill patients, no difference in short-term mortality was observed. In the largest and most recent RCT - EMPIRICUS – there was also no difference in outcome between patients receiving empiric antifungal therapy (micafungin) and patients receiving placebo (174). The overall quality of evidence was low, and treatment with empiric antifungals may be associated with increased costs.

While patients with sepsis or septic shock may not in general benefit from empiric antifungals, some patients with particular risk factors for fungal infection may, for example patients with febrile neutropenia who fail to defervesce after 4-7 days of broad-spectrum antibacterial therapy are at increased risk of having fungal disease [Table 2] (175, 176). The risk of *candida* sepsis or septic shock for other immunosuppressed populations is highly disease- and therapy-specific. Importantly, the decision to start empiric antifungal therapy depends on the type and number of risk factors, along with the local epidemiology of fungal infections.

Accordingly, we suggest using empiric antifungal therapy in patients at high risk of fungal infection, while we suggest avoiding this if the risk is low. The choice of antifungal agent for empiric therapy depends on multiple issues including host factors, prior colonization and infection, prior exposure to prophylactic or therapeutic antifungal therapy, comorbidities, and the toxicities and drug interactions of the therapeutic options.

Table 4. Examples of risk factors for fungal infection. The decision to start empirical antifungal therapy depends on the type and number of risk factors, along with the locale epidemiology of fungal infections.

|  |
| --- |
| **Risk Factors for Candida Sepsis** |
| Candida Colonization at Multiple Sites (177-179) |
| Surrogate Markers Such as Serum Beta-D-Glucan assay (177) |
| Neutropenia(180, 181) |
| Immunosuppression (173, 180, 181) |
| Severity of illness (High APACHE score) (182, 183) |
| Longer ICU length of stay (183) |
| Central Venous Catheters and Other Intravascular Devices (168, 180, 181, 184) |
| Persons Who Inject Drugs (185) |
| Total Parenteral Nutrition (186) |
| Broad Spectrum Antibiotics (178, 187) |
| Gastrointestinal Tract Perforations and Anastomotic Leaks (186, 188-190) |
| Emergency gastrointestinal or hepatobiliary surgery (190) |
| Acute Renal Failure and Hemodialysis (186, 188) |
| Severe Thermal Injury (191-193) |
| Prior surgery (186) |
|  |
| **Risk Factors for Endemic Yeast (Cryptococcus, Histoplasma, Blastomyces, Coccidioidomycosis)** |
| Antigen Markers Such as Cryptococcal, Histoplasma or Blastomyces assays (194-196) |
| HIV Infection (197-200) |
| Solid Organ Transplantation (199, 201-203) |
| High Dose Corticosteroid Therapy (199) |
| Hematopoietic Stem Cell Transplantation (204) |
| Certain Biologic Response Modifiers (205, 206) |
| Diabetes Mellitus (207) |
|  |
| **Risk Factor for Invasive Mold Infection** |
| Neutropenia (204, 208) |
| Surrogate Markers Such as Serum or Bronchoalveolar Lavage Galactomannan Assay (209-211) |
| Hematopoietic Stem Cell Transplantation (204, 208, 212) |
| Solid Organ Transplantation (202, 212-214) |
| High Dose Corticosteroid Therapy (215, 216) |
| Certain Biologic Response Modifiers (206, 217, 218) |

## Antiviral therapy

|  |
| --- |
| Recommendations |
| 1. We make no recommendation on the use of antiviral agents. |

**Rationale**

Viral infections encompass a broad spectrum of pathogens and diseases in humans but - apart from specific clinical situations such as epidemics/pandemics - are rarely the primary cause of sepsis. In a recent large international point prevalence study, viruses were documented in less than 4% of infections (133).

Historically, influenza has been one of the more common viral causes of sepsis. However, it is unclear to what extent the primary viral infection as opposed to bacterial pneumonia co-infection is the cause of organ dysfunction in these patients (219-222). More recently, SARS-CoV-2 (causing COVID-19) is now responsible for many cases of infection and sepsis (223). The ongoing pandemic due to SARS-CoV-2 has resulted in the understanding of this condition changing very rapidly (224).

While there appears to be no overall effect of neuraminidase inhibitors on mortality in patients with influenza-related pneumonia, there may be an effect when administered early in the course of the disease (225). For detailed information on specific antiviral therapy, including for influenza and SARS CoV-2, please refer to dedicated clinical practice guidelines (226-228).

Immunocompromised patients are particularly vulnerable to viral infections, including patients with neutropenia, human immunodeficiency virus (HIV) infection, haematological malignancies and hematopoietic stem cell transplantation or solid organ transplants; in these patients herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and respiratory viruses such as adenoviruses, can cause severe disease (229). Tropical and subtropical regions have endemic and epidemic outbreaks of zoonotic viral infections including those caused by Dengue, Ebola, Lassa, Marburg, Sin Nombre and Chikungunya virus. Many of these can manifest with clinical signs of sepsis, particularly in their early stages. Unfortunately, effective therapies are lacking for most of these viruses.

The desirable effects of empiric antiviral therapy are unknown, and as for other antimicrobial agents there is a risk of undesirable effects (165). Data on cost effectiveness were not available.

Due to the rapidly changing position related to antiviral therapies in critically ill patients presenting with several acute respiratory failure, this panel decided not to issue a recommendation on antiviral therapies and to refer the reader to more specific guidelines (226).

## Delivery of antibiotics

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we suggest using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion.   *Weak recommendation, moderate quality of evidence.* |

**Rationale**

Beta-lactam antibiotics may be subject to changes in important pharmacokinetic parameters in the setting of sepsis and septic shock resulting in sub-therapeutic concentrations (230, 231). As opposed to conventional intermittent infusion (infusion <30 minutes), administration by prolonged IV infusion, either as an extended infusion (antibiotic infused over at least half of the dosing interval) or as a continuous infusion, results in sustained beta-lactam concentrations which align with the pharmacodynamics of these drugs.

Two meta-analyses reported similar results supporting reduced short-term mortality (RR 0.70; 95% CI 0.57 - 0.87) with prolonged infusion of beta-lactams (232, 233).

No trials assessed the undesirable effects of continuous infusion, and the desirable effects were deemed important, while the overall quality of evidence was moderate. Prolonged infusion is a feasible intervention if suitable IV access is present, and resources are available to ensure the beta-lactam is infused over the necessary duration. The latter may be an issue in some resource limited settings, including LMICs.

Administration of a loading dose of antibiotic before prolonged infusion is essential to avoid delays to achieving effective beta-lactam concentrations (234). Over the course of therapy, both extended and continuous infusions will occupy a venous catheter/lumen more than an intermittent infusion and drug-stability and drug-drug compatibility considerations are important to ensure effectiveness of antibiotic and other IV drug therapies (235).

The reduction in short-term mortality from prolonged infusion of beta-lactams is significant with the intervention being feasible with negligible cost implications and no data suggesting inferior outcomes with prolonged infusion. Accordingly, we suggest prolonged infusion of beta-lactams over conventional bolus infusion in patients with sepsis and septic shock if the necessary equipment is available. Further research is needed on long-term outcomes, on the effect on emergence of antimicrobial resistance, and on costs of prolonged versus bolus infusion of beta-lactams (236).

## Pharmacokinetics and pharmacodynamics

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties.   *Best practice Statement.* |

**Rationale**

Antibiotics are subject to changes in PK/PD parameters in sepsis and septic shock where resultant concentrations may be too low risking clinical failure, or too high leading to toxicity [Table 3] (237-239). Augmented renal clearance (240), AKI (241), hypoalbuminemia (242), RRT (243) (244), and extracorporeal membrane oxygenation (245, 246) are examples of common scenarios that affect the concentrations of some antibiotics. Administration of antibiotics using an approach that adheres to PK/PD principles and using dosing regimens developed in patients with sepsis and septic shock is more likely to result in effective and safe drug concentrations compared to use of dosing recommendations provided in the manufacturer’s product information (247).

We did not identify any relevant data quantifying the value of dosing based on PK/PD principles in adults with sepsis and septic shock. Although there are no data on this topic directly derived from adults with sepsis and septic shock, data from a broader patient population, critically ill patients, support an increased likelihood of achieving effective and safe antibiotic concentrations when applying PK/PD principles to dosing (248). The application of PK/PD principles can be aided by clinical pharmacists (249). Some studies in critically ill patients have reported benefits in terms of clinical cure (237, 250-253).

Applying a PK/PD approach to antibiotic dosing requires support from knowledgeable clinician team members (254), use of a patient population-specific guideline document (255), use of therapeutic drug monitoring (256), and/or use of dosing software (238, 248). Some of these potential approaches to application of PK/PD-based dosing require extra resources, some of which may not be available in all settings, in which case freely available resources such as dosing nomograms can be used (234, 257, 258). Guidance on how to apply a PK/PD approach for specific drug classes have been described elsewhere (237). Further research is needed on short- and long-term mortality outcomes, effect on emergence of antimicrobial resistance, impact on drug stability within prolonged infusions and health economics of different PK/PD-based approaches to dosing.

Table 5. Guidance for PK/PD based dosing for specific drug classes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug or drug class** | **PK/PD index associated with bacterial killing or efficacy** | **Drug concentration target** | **Considerations for optimised dosing\*** | **Reference** |
| **Antibacterials** | | | | |
| Aminoglycosides | AUC0-24/MIC; Cmax/MIC | AUC 70-100  Cmax/MIC 8-10 | Use extended interval dosing with patient weight and kidney function | (237) |
| Beta-lactams | *f*T>MIC | Cmin > MIC | Use prolonged infusions, consider patient weight and kidney function | (253) |
| Colistin | AUC0-24/MIC | Unspecified | Use patient weight and kidney function | (259) |
| Daptomycin | AUC0-24/MIC; Cmax/MIC | AUC0-24/MIC > 200 | Use patient weight and kidney function | (237) |
| Fluoroquinolones | AUC0-24/MIC; Cmax/MIC | AUC0-24/MIC 80-125 | Use kidney function | (237) |
| Vancomycin | AUC0-24/MIC | AUC0-24/MIC 400 | Use patient weight and kidney function | (260) |
| **Antifungals** | | | | |
| Fluconazole | AUC0-24/MIC | AUC0-24/MIC 100 | Use patient weight and kidney function | (261) |
| Posaconazole | AUC0-24/MIC | Cmin 1-4 mg/L | Use formulation-specific dose | (261) |
| Voriconazole | AUC0-24/MIC | Cmin 2-6 mg/L | Use patient weight | (261) |

\* Other considerations than those listed may have been listed in studies in critically ill patient sub-populations

**Legend**: AUC0-24 – ratio of area under the concentration-time curve from 0-24 hours; MIC – minimum inhibitory concentration; *f*T>MIC – time overdosing interval that free (unbound) drug is maintained above the MIC; Cmax – maximum concentration in a dosing interval; Cmin – minimum concentration in a dosing interval

**Note**: use of therapeutic drug monitoring has been described for all drugs, although it is not widely available for most.

## Source control

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we recommend rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical.   *Best practice Statement.* |

**Rationale**

Appropriate source control is a key principle in the management of sepsis and septic shock (12, 13). Source control may include drainage of an abscess, debriding infected necrotic tissue, removal of a potentially infected device, or definitive control of a source of ongoing microbial contamination (262). Foci of infection readily amenable to source control include intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotizing soft tissue infection, other deep space infection (e.g. empyema or septic arthritis), and implanted device infections (262).

Source control of infectious foci was associated with improved survival in recent observational and cluster randomized studies (120, 263, 264). Source control should be achieved as soon as possible following initial resuscitation (265, 266). While there are limited data to conclusively issue a recommendation regarding the timeframe in which source control should be obtained, smaller studies suggest that source control within 6 to 12 hours is advantageous (265-271). Studies generally show reduced survival beyond that point. The failure to show benefit with source control implemented in less than 6 hours may be a consequence of the limited number of patients and the heterogeneity of the intervention. Therefore, any required source control intervention in sepsis and septic shock should ideally be implemented as soon as medically and logistically practical after the diagnosis is made (120). Clinical experience suggests that without adequate source control, many severe presentations will not stabilize or improve despite rapid resuscitation and provision of appropriate antimicrobials. In view of this fact, prolonged efforts at medical stabilization in lieu of source control for severely ill patients, particularly those with septic shock, are generally not advised (272).

The selection of optimal source control methods must weigh the benefits and risks of the specific intervention, the patient’s preference, clinician’s expertise, availability, risks of the procedure, potential delays, and the probability of the procedure’s success. In general, the least invasive option that will effectively achieve source control should be pursued. Open surgical intervention should be considered when other interventional approaches are inadequate or cannot be provided in a timely fashion. Surgical exploration may also be indicated when diagnostic uncertainty persists despite radiologic evaluation, when the probability of success with a percutaneous procedure is uncertain, or when the undesirable effects of a failed procedure are high. Logistic factors unique to each institution, such as surgical or interventional staff availability, may also play a role in the decision. Future research is needed to investigate the optimal timing and method of source control in patients with sepsis and septic shock with a source of infection amenable to drainage.

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.   *Best practice Statement.* |

**Rationale**

Removal of a potentially infected intravascular access device is considered a part of adequate source control (262). An intravascular device suspected to be a source of sepsis should be removed after establishing another site for vascular access and following successful initial resuscitation (265, 266). In the absence of septic shock or fungemia, some implanted tunnelled catheter infections may be treated effectively with prolonged antimicrobial therapy if removal of the catheter is not practical (273). However, catheter removal with adequate antimicrobial therapy is definitive and is the preferred treatment in most cases.

We identified one relevant RCT (274) and two observational studies (275, 276). There was no evidence of a difference in mortality, however, the studies were hampered by significant limitations, including risk of confounding by indication (the observational studies) and imprecision (the RCT), which is why the results should be interpreted cautiously. The quality of evidence was very low.

## De-escalation of antibiotics

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation*.*   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Antimicrobial exposure is linked to the development of antimicrobial resistance and efforts to reduce both the number of antibiotics administered and their spectrum of therapy are therefore important strategies in patients with sepsis and septic shock (165). This is particularly relevant in empiric therapy where broad-spectrum therapy is recommended, as the causative pathogen has not yet been identified. Once both the pathogen(s) and susceptibilities are known, antimicrobial de-escalation - i.e., stopping an antimicrobial that is no longer necessary (in case of combination therapy) or changing an antimicrobial to narrow the spectrum is encouraged. Given the adverse societal and individual risks to continued unnecessary antimicrobial therapy, thoughtful de-escalation of antimicrobials based on adequate clinical improvement is appropriate even if cultures are negative. Early discontinuation of all antimicrobial therapy if infection is ruled out is advisable (277). Antimicrobial de-escalation should ideally be done as soon as possible, and rapid diagnostic techniques may facilitate this.

We identified direct evidence from 13 studies (1,968 patients) (277), including 1 RCT (278). In our meta-analysis, we observed improved short-term mortality in patients who were de-escalated (RR 0.72; 95% CI 0.57 to 0.91) (supplementary appendix 2). Long-term mortality was evaluated in one study only and did not demonstrate a difference (RR 0.99; 95% CI 0.64 to 1.52). De-escalation was associated with shorter length of stay in the hospital (MD -5.56 days; 95% CI -7.68 to -3.44), but not in the ICU (MD -2.6 days; 95% CI -5.91 to 0.72).

Most studies were observational, and there are concerns that de-escalation is used primarily in patients who are getting better, which is why the reported improved short-term mortality should be interpreted with caution (277, 279).

De-escalation is in generally safe, may offer cost savings when unnecessary antibiotics are discontinued, and reduced risk of antimicrobial resistance and reduced toxicity and side-effects may be important (280). Based on the overall very low quality of evidence, RCTs are warranted along with more studies on antimicrobial resistance.

## Duration of antibiotics

|  |
| --- |
| Recommendation |
| 1. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest using shorter over longer duration of antimicrobial therapy.   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Restricting antimicrobial therapy to the shortest course associated with better outcomes is an important part of antimicrobial stewardship (281-285). The optimal duration of antimicrobial therapy for a given patient with sepsis or septic shock depends on many factors, including host, microbe, drug, and anatomical site [Table 4] (99, 100).

There have been considerable efforts over the past two decades to clarify the optimal duration of antimicrobial therapy by comparing “short” courses with traditional (“longer”) courses. There are data from RCTs in specific conditions such as pneumonia (286-289), urinary tract infections (290), bacteremia (291, 292), and intraabdominal infections (293). In many of the trials, the shorter course was just as effective as the longer course but associated with fewer adverse consequences. Very few trials, however, focused exclusively on critically ill patients with sepsis or septic shock, and the overall quality of evidence was very low.

Given the lack of definitive and generalizable data regarding the optimal duration of therapy for patients who are critically ill, it is not surprising that there is considerably practice variation (281, 294). Specialist consultation appears to be associated with improved patient outcomes for a variety of infectious syndromes (295-300). This has generally been ascribed to improvements in microbial appropriateness of the empiric antimicrobial regimen provided. However, it is also possible that reducing the duration of unnecessary therapy may account for at least part of the benefit.

Thus, for adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest a shorter course of antibiotics, as this is less costly, has fewer undesirable effects without impacting adversely on outcomes.

Table 6. Planned duration of empirical antimicrobial therapy in RCTs of shorter versus longer duration of therapy according to clinical syndrome.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Population/syndrome** | **RCT (data extracted from)** | **Shorter duration** | **Longer duration** | **Outcomes** |
| Pneumonia | Capellier 2012 (301) | 8 days | 15 days | No difference |
| Chastre 2003 (301, 302) | 8 days | 15 days | No difference |
| El Moussaoui 2006 (302) | 3 days | 8 days | No difference |
| Fekih Hassen 2009 (301-303) | 7 days | 10 days | No difference |
| File 2007 (302, 303) | 5 days | 7 days | No difference |
| Kollef 2012 (302, 303) | 7 days | 10 days | No difference |
| Leophonte 2002 (302, 303) | 5 days | 10 days | No difference |
| Medina 2007 (301) | 8 days | 12 days | No difference |
| Siegel 1999 (302, 303) | 7 days | 10 days | No difference |
| Tellier 2004 (302, 303) | 5 days | 7 days | No difference |
| Bacteremia | Chaudhry 2000 (302) | 5 days | 10 days | No difference |
| Runyon 1991 (302) | 5 days | 10 days | No difference |
| Yahav 2018 (304) | 7 days | 14 days | No difference |
| Intra-abdominal infection | Montravers 2018 (305) | 8 days | 15 days | No difference |
| Sawyer 2015 (293) | Max. 5 days | Max. 10 days | No difference |
| Urinary tract infection | Peterson 2008 (290) | 5 days | 10 days | No difference |

## Biomarkers to discontinue antibiotics

|  |
| --- |
| Recommendations |
| 1. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Shorter durations of antimicrobial therapy are in general recommended; however, critically ill patients often receive antimicrobials for more days than necessary (288, 301, 306). While typically clinical evaluation alone is used to decide duration, biomarkers could offer additional information. C Reactive Protein is often used in this regard. Procalcitonin has been studied most extensively both in critically ill and non-critically ill patients, both for initiation and discontinuation of therapy (307).

We identified direct evidence from 14 RCTs (n=4,499 patients) that assessed use of procalcitonin to guide antimicrobial treatment duration in patients with sepsis (two trials included critically ill patients in general) (308-321). A meta-analysis suggested improved mortality in patients who were managed using procalcitonin versus control (RR 0.89; 95% CI 0.80 to 0.99), while there was no effect on length of stay in ICU or hospital. Antibiotic exposure was consistently lower in patients who were managed with procalcitonin and clinical evaluation, however, in many trials the total duration of therapy was still 7 days or longer in the intervention group. Also, the algorithms for antimicrobial therapy, frequency of procalcitonin monitoring and the thresholds (or percentage change in procalcitonin concentration) for discontinuation differed across the trials. Therefore, the overall quality of evidence was judged to be low.

The undesirable effects of using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials are considered minimal, and do not outweigh the potential benefits (322). Limited data on the cost-effectiveness are available, although a single center study reported decreased hospital costs associated with PCT-guided antibiotic in medical ICU patient with undifferentiated sepsis (323). Procalcitonin testing may not be available in all countries and healthcare settings, including LMICs.

Based on apparent benefit and no obvious undesirable effects, we suggest using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials in adults with an initial diagnosis of sepsis or septic shock and adequate source control, if the optimal duration of therapy is unclear and if procalcitonin is available.

# HEMODYNAMIC MANAGEMENT

## Fluid management

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.   *Strong recommendation, moderate quality of evidence.* |
| 1. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.   *Weak recommendation, low quality of evidence.* |
| 1. For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids over using crystalloids alone.   *Weak recommendation, moderate quality of evidence.* |
| 1. For adults with sepsis or septic shock, we recommend against using starches for resuscitation.   *Strong recommendation, high quality of evidence.* |
| 1. For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation.   *Weak recommendation, moderate quality.* |

**Rationale**

Fluid therapy is a key part of the resuscitation of sepsis and septic shock. Crystalloids have the advantage of being inexpensive and widely available. The absence of clear benefit following the administration of colloids compared to crystalloid solutions supports the use of crystalloid solutions in the resuscitation of patients with sepsis and septic shock (324). The optimal fluid remains a subject of debate. For decades, the administration of normal saline solution (0.9% sodium chloride) has been common practice (325), but potential adverse effects that include hyperchloremic metabolic acidosis, renal vasoconstriction, increased cytokine secretion and concern about AKI have led to increased interest in chloride-restrictive solutions, known as balanced or buffered solutions (326-330). Subsequently, a network meta-analysis of 14 RCTs of patients with sepsis showed in an indirect comparison that balanced crystalloids were associated with decreased mortality, compared to saline (331).

There have been a number of recent RCTs assessing the question of which crystalloid may be most beneficial in patients with sepsis. In the SPLIT multicenter, double-blinded clinical trial, the comparison between balanced solutions and normal saline yielded no differences in mortality or AKI (332). The modest volume of infused fluid, the predominance of surgical patients, and the low number of septic patients (4%) precludes generalizability of the results. In 2016, the SALT pilot trial (n=974) compared balanced solutions versus normal saline; with septic patients comprising 25% and 28% of the population, respectively (333). The primary outcome, a composite outcome including mortality, new RRT or persistent renal dysfunction (major adverse kidney event within 30 days, MAKE30), was similar between groups (24.6% vs. 24.7%). Subsequently, the SMART trial was published in 2018, a single-center, multiple-crossover study including 15,802 patients who received balanced solutions or normal saline, alternating on a monthly basis (334). In the pre-specified subgroup of patients admitted with sepsis in all participating ICUs, 30-day mortality was lower in those receiving balanced solutions, compared to normal saline (OR 0.80; 95% CI 0.67−0.94). Likewise, in a secondary analysis including only the 1,641 patients admitted to medical ICUs with a diagnosis of sepsis, balanced solutions were associated with reduced 30-day hospital mortality (OR 0.74; 95% CI 0.59 – 0.93) and MAKE30, and increased vasopressor- and RRT- free days (335).

The SMART trial was a single-center study without individual patient randomization and no blinded assignment of the intervention, it exposed participants to moderate amount of fluid volume, identification of sepsis subgroups was based on ICD-10 codes, and it used a composite outcome which may not be as relevant as a patient-centered outcome (336). However, the use of balanced solutions in sepsis may be associated with improved outcomes compared with chloride-rich solutions. No cost-effectiveness studies compared balanced and unbalanced crystalloid solutions. Therefore, we considered the desirable and undesirable consequences to favor balanced solutions, but as the quality of the evidence is low, we issued a weak recommendation. Two ongoing large RCTs will provide additional data and inform future guideline updates (337, 338).

Although albumin is theoretically more likely to maintain oncotic pressure than crystalloids (339), it is more costly and there is no clear benefit with its routine use. Since the publication of the 2016 guidelines (12) two single-center trials and two meta-analyses have been published on this topic (324, 340-342). A Cochrane review including RCTs with 12,492 patients comparing albumin versus crystalloids found no difference in 30-day (RR 0.98 ; 95% CI 0.92 - 1.04 ) or 90-day mortality (RR 0.98; 95% CI 0.92 - 1.04) or need for RRT between groups (RR 1.11; 95% CI 0.96 - 1.27) (324). This meta-analysis included patients with critical illness, and while the main solution included in the analysis was albumin, some studies in other analyses included fresh frozen plasma. A second meta-analysis, which also included critically ill patients, found lower static filling pressures (MD -2.3 cm H2O; 95% CI 3.02 -1.05) and mean arterial pressure (MAP) (MD -3.53 mmHg; 95% CI -6.71 to -0.36) with crystalloid use, but no difference in mortality at 28 days (RR 1.0; 95% CI 0.92 - 1.10) or 90 days (RR 1.32; 95% CI 0.76 - 2.29) (340). The largest clinical trial in sepsis, the ALBIOS trial comparing a combination of albumin and crystalloids to crystalloids alone in 1818 patients with sepsis or septic shock did not demonstrate a difference in 28-day (RR 1.0; 95% CI, 0.87-1.14) or 90-day mortality (RR 0.94; 95% CI 0.85 - 1.05) (339). Of note, in this trial, albumin was given as a 20% solution, with a treatment goal of a serum albumin concentration of 30 g/L until ICU discharge or 28 days. A meta-analysis of studies including septic patients did not show a significant difference in mortality (RR 0.98; 95% CI 0.89-1.08). In addition, the risk of new organ failures (RR 1.02; 95% CI 0.93 to 1.11), ventilator-free days or vasopressor-free days did not differ. Although albumin use resulted in a larger treatment effect in the septic shock subgroup (RR 0.88; 95% CI 0.77-0.99) than in the sepsis subgroup (RR 1.03; 95% CI 0.91-1.17), the subgroup analysis did not detect a subgroup effect (P-interaction= 0.19).

The lack of proven benefit and higher cost of albumin compared to crystalloids contributed to our strong recommendation for the use of crystalloids as first-line fluid for resuscitation in sepsis and septic shock. The suggestion to consider albumin in patients who received large volumes of crystalloids is informed by evidence showing higher blood pressure at early and later time points (339), higher static filling pressures (340), and lower net fluid balance (339) with albumin. Limited data precludes a cutoff value for crystalloid infusion above which albumin might be considered as part of resuscitation.

In the 2016 SSC guidelines, a strong recommendation was issued against using hydroxyethyl starch (HES) (12). No new data were identified. A previous meta-analysis of RCTs in septic patients showed a higher risk of RRT with the use of HES 130/0.38-0.45 (RR 1.36; 95% CI 1.08–1.72) and a higher risk of death in a pre-defined analysis of low risk of bias trials (RR 1.11; 95% CI 1.0 – 1.2) (343). A network meta-analysis of patients with sepsis or septic shock also demonstrated a higher risk of death (OR 1.1; 95% CI 0.99–1.30) and need for RRT (OR 1.39; 95% CI 1.17–1.66) (331) with starches in a direct comparison with crystalloids. Therefore, the 2016 recommendation against the use of HES in resuscitation of patients with sepsis or septic shock did not change (331, 343).

Gelatin is a synthetic colloid used as a resuscitation fluid; there is a lack of powered well-designed studies supporting its administration in sepsis and septic shock. Included studies are generally small and include mostly post-operative, non-critically ill patients. In an indirect comparison, a 4-node network meta-analysis conducted in patients with sepsis, showed no clear effect on mortality when compared to crystalloids (OR 1.24; 95% credible interval [CrI] 0.61–2.55) (331). Similarly, another RCT did not find an effect on mortality with gelatin use (RR 0.87; 95% CI 0.66 – 1.12) (344). Adverse effects of gelatin have been reviewed in a network meta-analysis, which demonstrated higher risk of RRT with gelatin use compared to normal saline (OR 1.27; 95% CrI 0.44–3.64) and balanced crystalloids (OR 1.50; 95% CrI 0.56–3.96) (345). Overall, the quality of evidence was moderate, due to imprecision and indirectness. In a systematic review of RCTs including patients with hypovolemia, gelatin use increased the risk of anaphylaxis (RR 3.01; 95% CI 1.27–7.14) in comparison with crystalloids use (346). Furthermore, gelatins may affect hemostasis and the effect on blood transfusions was unclear (RR 1.10; 95% CI 0.86-1.41). Therefore, in the face of inconclusive effect on mortality, increased adverse effects, and higher costs, the panel issued a weak recommendation against the use of gelatin for acute resuscitation. More high-quality studies are needed to inform future guideline updates.

## Vasopressors

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors. *Strong recommendation*   Dopamine. H*igh quality evidence*  Vasopressin. M*oderate quality evidence*  Epinephrine. L*ow quality evidence*  Selepressin. *Low quality evidence*  Angiotensin 2. *Very low-quality evidence*  Remark  In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine. |
| 1. For adults with septic shock on norepinephrine with inadequate MAP levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine.   *Weak recommendation, moderate quality evidence.*  Remark:  In our practice, vasopressin is usually started when the dose of norepinephrine is in the range of 0.25-0.5 μg/kg/min. |
| 1. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine.   *Weak recommendation, low quality evidence.* |
| 1. For adults with septic shock, we suggest against using terlipressin.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Norepinephrine is a potent α-1 and β-1 adrenergic receptors agonist, which results in vasoconstriction and increased MAP with minimal effect on heart rate. Dopamine acts in a dose-dependent fashion on dopamine-1, α-1 and β-1 adrenergic receptors. At lower dosages, dopamine causes vasodilation via dopamine-1 receptor activity in the renal, splanchnic, cerebral, and coronary beds. With higher dosages, dopamine’s α-adrenergic receptor activity predominates resulting in vasoconstriction and increased systemic vascular resistance (SVR); its β-1 adrenergic receptor activity can lead to dose-limiting arrhythmias. Norepinephrine is more potent than dopamine as a vasoconstrictor. In a systematic review and meta-analysis of 11 RCTs, norepinephrine resulted in a lower mortality (RR 0.89; 95% CI 0.81 – 0.98) and lower risk of arrhythmias (RR 0.48; 95% CI 0.40 – 0.58) compared with dopamine (347). Although the β-1 activity of dopamine may be useful in patients with myocardial dysfunction, the higher risk of arrhythmias limits its use (348).

Epinephrine’s action is also dose-dependent with potent β-1 adrenergic receptor activity and moderate β-2 and α-1 adrenergic receptor activity. The activity of epinephrine, at low doses, is primarily driven by its action on β-1 adrenergic receptors, resulting in increased cardiac output (CO), decreased systemic vascular resistance (SVR) and variable effects on MAP. At higher doses, however, epinephrine administration results in increased SVR and CO. Potential adverse effects of epinephrine include arrhythmias and impaired splanchnic circulation (349). Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β-2 adrenergic receptors, making the use of serum lactate to guide resuscitation challenging (350). A randomized blinded study comparing epinephrine with norepinephrine in patients with shock showed no difference in 90-day mortality (HR 0.88; 95% CI 0.63 – 1.25) and vasopressor-free days (351). The panel issued a strong recommendation for norepinephrine as the first-line agent over other vasopressors (figure 2).

Vasopressin is an endogenous peptide hormone produced in the hypothalamus and stored and released by the posterior pituitary gland. Its mechanism for vasoconstrictive activity is multifactorial and includes binding of V1 receptors on vascular smooth muscle resulting in increased arterial blood pressure. Studies show that vasopressin concentration is elevated in early septic shock but decreases to normal range in the majority of patients between 24 and 48 hours as shock continues (352, 353). This finding has been called “relative vasopressin deficiency” as, in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. Unlike most vasopressors, vasopressin is not titrated to response, but it is usually administered at a fixed dose of 0.03 units/minute for the treatment of septic shock. In clinical trials, vasopressin was used up to 0.06 units/minute (354). Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia (355).

The VANISH trial directly compared the use of vasopressin versus norepinephrine by randomizing patients with septic shock in a factorial 2 × 2 design aiming to also assess the role of hydrocortisone. There was no significant difference between the vasopressin and norepinephrine groups in 28-day mortality [30.9% vs 27.5%; RR 1.13 (95%CI 0.85 – 1.51). Although there was no difference with respect to kidney injury (RR 0.89; 95%CI 0.72 – 1.11), vasopressin use reduced the risk of RRT (RR 0.71; 95%CI 0.53 – 0.97) (354).

As for combination therapy, the main study (the VASST trial) comparing norepinephrine alone to norepinephrine plus vasopressin (0.01-0.03 U/min) showed no improvement in 28-day mortality (39.3% vs 35.4%, P=0.26) (356). However, in a subgroup analysis, patients with less severe shock receiving norepinephrine <15 μg/min had improved survival with the addition of vasopressin (26.5% vs. 35.7%, P=0.05). Both VANISH and VASST demonstrated a catecholamine-sparing effect of vasopressin; as such, the early use of vasopressin in combination with norepinephrine may help reduce the adrenergic burden associated with traditional vasoactive agents (357). In our systematic review of 10 RCTs, vasopressin with norepinephrine reduced mortality as compared to norepinephrine alone (RR 0.91; 95% CI 0.83 – 0.99) but did not reduce the need for RRT (RR 0.79; 95% CI 0.57 – 1.10). There was no difference in the risks of digital ischemia (RR 1.01; 95% CI 0.33 – 9.84) or arrhythmias (RR 0.88; 95% CI 0.63 – 1.23). The threshold for adding vasopressin varied among studies and remains unclear. Starting vasopressin when norepinephrine dose is in the range of 0.25-0.5 μg/kg/min seems sensible (354). Another meta-analysis of RCTs on distributive shock showed a lower risk of atrial fibrillation with the combination of vasopressin and norepinephrine compared to norepinephrine alone (358). However, a recent individual patient data meta-analysis of patients with septic shock from 4 RCTs showed that vasopressin alone or in combination with norepinephrine led to higher risk of digital ischemia (risk difference [RD] 1.7%; 95% CI 0.3 - 3.2) but lower risk of arrhythmia (RD −2.8%; 95% CI −0.2 to −5.3) compared to norepinephrine alone (359).

The evidence regarding the optimal therapeutic strategy for shock requiring high dose vasopressors is scant (360). Epinephrine has been suggested as second or third-line vasopressor for patients with septic shock. With the use of norepinephrine at elevated concentrations, the α1 receptors may already be saturated and downregulated (361). Thus, the use of another drug such as epinephrine that targets the same receptors may be of limited utility and vasopressin could be more adequate in this scenario. In an indirect comparison, a network meta-analysis did not find any significant difference between epinephrine and vasopressin in terms of mortality (RR 0.94; 95% CI 0.47 – 1.88) (362). Epinephrine might be useful in refractory septic shock patients with myocardial dysfunction.

Thus, we considered the desirable and undesirable consequences of these vasopressors and issued a strong recommendation to use norepinephrine as a first line agent instead of dopamine, vasopressin, epinephrine and selepressin and angiotensin 2 in patients with septic shock as a first-line agent, and a weak recommendation over selepressin and angiotensin 2. Although some evidence suggests that vasopressin might be superior to norepinephrine in terms of clinical outcomes, the panel took into consideration its higher costs and lower availability and have issued a strong recommendation to use norepinephrine as first line agent instead of vasopressin. We also consider the potential benefit and undesirable consequences of using the combination of norepinephrine and vasopressin and issue a weak recommendation for adding vasopressin instead of escalating the dose of norepinephrine. Further evidence is needed to properly address the role of combination therapy of vasopressors in septic shock.

The panel also recognized that availability of, and experience with, norepinephrine may vary. As part of the global campaign for universal healthcare, the World Health Organization (WHO) essential medicines and health products program works to increase global access to essential, high-quality, safe, effective, and affordable medical products. If norepinephrine is unavailable, either dopamine or epinephrine can be used with special attention given to the risk of arrhythmias.

Selepressin is a highly selective V1 agonist, inducing vasoconstriction via stimulation of vascular smooth muscle. It does not share the typical V1b and V2 receptor effects of vasopressin (increased pro-coagulant factors, salt, and water retention, nitric oxide, and corticosteroid release) and has, therefore, been postulated as a potentially attractive non-catecholamine vasopressor alternative to norepinephrine. Selepressin has been studied in two randomized trials in septic shock. The first, a double-blind, randomized, placebo-controlled phase IIa trial, compared three ascending doses of selepressin (1.25, 2.5 and 3.75 ng/kg/min) in maintaining blood pressure, with open-label norepinephrine (363). Selepressin at a dose of 2.5 ng/kg/min was demonstrated to be effective in maintaining MAP >60 mmHg without norepinephrine in about 50% of patients at 12 hours and about 70% of patients at 24 hours. A follow-on phase IIb/phase III trial using an adaptive design, initially comparing three doses (1.7, 2.5 and 3.5 ng/kg/min) with the potential to add a further 5 ng/kg/min dose group (364). The study was stopped for futility after enrolment of 828 patients, with no significant differences between any of the key endpoints [ventilator- and vasopressor-free days, 15.0 (selepressin) versus 14.5 (placebo), P=0.30; 90-day all-cause mortality, 40.6% vs 39.4%, P=0.77; 30-day RRT-free days, 18.5 vs 18.2, P=0.85; 30-day ICU-free days, 12.6 vs 12.2, P=0.41]; adverse event rates were also similar between groups. The meta-analysis of the 2 studies did not show significant difference in mortality (selepressin: 41.8% vs norepinephrine: 40.45%; RR 0.99 (95% CI 0.84 – 1.18)). As selepressin failed to demonstrate clinical superiority over norepinephrine, we considered the desirable and undesirable consequences to be in favor of norepinephrine and issued a weak recommendation against the use of selepressin as a first-line therapy. Furthermore, it is not currently commercially available.

Angiotensin II is a naturally occurring hormone with marked vasoconstrictor effects, triggered through stimulation of the renin-angiotensin system. A synthetic human preparation has recently become available for clinical use and has been studied in two clinical trials. After a small, short-term pilot of 20 patients with vasodilatory (septic) shock (10 patients in each group) which showed physiological efficacy without obvious safety issues (365), a larger RCT of 344 patients was performed in patients with vasodilatory shock (approximately 90% confirmed or presumed sepsis) (366). The primary endpoint, an increase of MAP of at least 10 mmHg or to at least 75mmHg, was achieved in 114 of 163 patients in the angiotensin II group and in 37 of 158 patients in the placebo group (69.9% vs 23.4%, P<0.001). A meta-analysis found no difference in mortality rates between angiotensin II and norepinephrine (46.2% vs 54.2%; RR 0.85 (95% CI 0.69 – 1.06); very low quality). There was no clear increase in adverse events with the use of angiotensin II. As the available evidence is of very low quality, and clinical experience in sepsis and, therefore, demonstration of safety remains limited, the panel considered that angiotensin should not be used as a first-line agent, but having demonstrated physiological effectiveness, it may have a role as an adjunctive vasopressor therapy.

Terlipressin is a prodrug and is converted to lysine vasopressin by endothelial peptidases, producing a “slow release” effect and giving an effective half-life of around 6 hours. Terlpressin is more specific for the V1 receptors and it has been studied in 9 clinical trials of patients with sepsis, with or without cirrhosis, involving 950 patients in total. Our meta-analysis showed no difference in mortality (terlipressin: 42.9% vs 49.0%; RR 0.89 (95% CI 0.70 – 1.13); low quality) but an increase in adverse events. The largest of these studies enrolled 617 patients with septic shock, in a randomized, blinded fashion, with terlipressin (or placebo) added at a dose of between 20 mcg/hr to 160 mcg/hr to a standard norepinephrine-based approach, to achieve a MAP of 65-75 mmHg (367). The primary outcome was death from any cause at 28 days. The 28-day mortality in the two groups was 40% for terlipressin and 38% for norepinephrine (OR 0.93; 95% CI 0.55 – 1.56, P=0.80), and there were no differences in SOFA score at day 7 or vasopressor free days. More patients who received terlipressin had serious adverse events; 33 of 260 (12%) patients experienced digital ischemia after receiving terlipressin, versus only one patient who received norepinephrine (P<0.0001); diarrhea was also more common in the terlipressin group (2.7% versus 0.35%, P=0.037). There were three cases of mesenteric ischemia in the terlipressin group versus one in the norepinephrine group. Therefore, the panel considered that the undesirable consequences are higher with the use of terlipressin and issued a weak recommendation against its use in patients with septic shock.

## Inotropes

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone.   *Weak recommendation, low quality of evidence.* |
| 1. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest against using levosimendan.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Sepsis-induced myocardial dysfunction is recognized as a major contributor to the hemodynamic instability and is associated with worse outcomes of patients with septic shock (368). Inotropic therapy can be used in patients with persistent hypoperfusion after adequate fluid resuscitation, and in patients with myocardial dysfunction, based on suspected or measured low CO and elevated cardiac filling pressures. Dobutamine and epinephrine are the most commonly used inotropes. Physiologic studies demonstrate that dobutamine increases CO and oxygen transport, increases splanchnic perfusion and tissue oxygenation, improves intramucosal acidosis and hyperlactatemia (369). However, these effects may not be predictable (370). Dobutamine infusion may produce severe vasodilation and result in lower MAP. In addition, the inotropic response may be blunted in sepsis with a preserved chronotropic effect causing tachycardia without an increase in stroke volume (SV) (370). No RCTs compared dobutamine to placebo in this population. Indirect comparison from network meta-analysis showed that dobutamine with norepinephrine had no clear impact on mortality when compared to no inotropic agents (OR 0.69; 95% CI 0.32 to 1.47) (362). None of the trials directly compared dobutamine combined with norepinephrine to norepinephrine alone. In an observational study of 420 patients with septic shock, the use of an inotropic agent (dobutamine, levosimendan, epinephrine, or milrinone) was independently associated with increased 90-day mortality (OR 2.29; 95% CI 1.33 to 3.94) even after after propensity score adjustment (371). However, the analysis adjusted only to baseline characteristics, without accounting for time-varying confounders including the patient condition at the time of initiating inotropes which may explain the association with mortality. The panel considered the network meta-analysis as a higher quality than observational studies and issued a suggestion to use inotropes only in selected situations.

No evidence supports the superiority of dobutamine over epinephrine. Epinephrine is commonly available especially in low-resource settings (372). In an indirect comparison of dobutamine versus epinephrine, a network meta-analysis showed no clear effect on mortality (OR 1.18; 95% CI 0.47-3.97) (362). Therefore, we considered the desirable and undesirable consequences to be comparable for both drugs and issued a weak recommendation to use either one for patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and MAP. Both should be discontinued in the absence of improvement in hypoperfusion or in the presence of adverse events. Further evidence derived from high quality RCTs is needed to properly address the role of inotropes in sepsis.

Levosimendan is a calcium-sensitizing drug with inotropic and vasodilatory properties. It has been evaluated in septic shock (373). A meta-analysis of 3 RCTs (n=781) showed that levosimendan, compared to no inotropic agents, did not impact mortality (RR 0.87; 95% CI 0.59 to 1.28). Data from the LeoPARDS trial (n=515) showed that levosimendan versus no inotropic agents was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrythmia (373). A meta-analysis of 7 RCTs comparing levosimendan with dobutamine showed that levosimendan was not superior to dobutamine in adults with sepsis in terms of mortality (OR 0.80; 95% CI 0.48, 1.33; p=0.39) (374). Thus, the panel issued a weak recommendation against the use of levosimendan based on the lack of benefit, in addition to the safety profile, cost and the limited availability of the drug.

## Monitoring and intravenous access

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock, we suggest using invasive monitoring of arterial blood pressure over non-invasive monitoring, as soon as practical and if resources are available.   *Weak recommendation, very low quality of evidence.* |
| 1. For adults with septic shock, we suggest starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured.   *Weak recommendation, very low quality of evidence.*  Remark  When using vasopressors peripherally, they should be administered only for a short period of time and in a vein in or proximal to the antecubital fossa. |

**Rationale**

Estimation of blood pressure using a non-invasive cuff tends to be inaccurate and the discrepancy more pronounced in shock states (375-379). Insertion of an arterial catheter permits safe, reliable and continuous measurement of arterial pressure and allows real time analysis so that therapeutic decisions can be based on immediate and accurate blood pressure information (380). A systematic review of observational studies showed that the risk of limb ischemia and bleeding was less than 1% for radial catheters, and the risk of limb ischemia and bleeding was less than 1% and 1.58%, respectively for femoral catheters. The most common complication was localized hematoma, 14% for radial and 6% for femoral catheters (381). Ultrasound guidance may increase the first attempt success rate and decrease the complication rate (382, 383). A systematic review showed higher risk of infections when femoral arterial catheters were used compared to radial artery catheters (RR 1.93; 95% CI 1.32–2.84), and the overall pooled incidence of bloodstream infection was 0.96 per 1000 catheter days (384). In the previous version of these guidelines, a weak recommendation was issued for using invasive monitoring of arterial blood pressure over non-invasive monitoring (12). Since then, no new relevant evidence became available. Large, randomized trials that compare arterial blood pressure monitoring versus non-invasive methods are still lacking. In view of the low complication rate and likely higher accuracy of blood pressure measurement, the benefits of arterial catheters probably outweigh the risks. However, the potentially limited resources in some countries and the lack of high-quality studies need to be considered. Therefore, the panel issued a weak recommendation in favor of arterial catheter placement. Arterial catheters should be removed as soon as continuous hemodynamic monitoring is no longer required to minimize the risk of complications.

The prompt initiation of vasopressors to restore blood pressure is an integral component of the management of septic shock. Vasopressors have been traditionally administered via a central venous access due to concerns of extravasation, local tissue ischemia and injury if administered peripherally. However, the process of securing central venous access can be time consuming and requires specialized equipment and training that may not be available in under resourced settings even in high income countries, leading to a delayed initiation of vasopressors (385). Large randomized trials that compare central and peripheral catheters for initial infusion of vasopressor are lacking. A small study (n = 263) randomly allocated patients to receive peripheral vascular access or a central access (386). The need for vasopressor was the indication for venous access in 70% of the patients. The incidence of major catheter-related complications was higher in those randomized to peripheral venous lines with no significant difference in the incidence of minor catheter-related complication. The most common peripheral venous line complication was difficulty in placement. Almost half of the patients assigned to the peripheral access group did not need a central line throughout their ICU stay. Other authors also showed that central lines could be avoided by peripheral line insertion (387). The administration of vasopressors through peripheral IV catheters is generally safe. A recent systematic review showed that extravasation occurred in 3.4% (95% CI 2.5-4.7%) of patients with no reported episodes of tissue necrosis or limb ischemia (388). Most of the studies reported no need for active treatment of the extravasation, and a systematic review concluded that most patients who experience extravasation events have no long-term sequelae (389). Extravasation may occur more frequently if vasopressors are infused distally to the antecubital fossa; a meta-analysis showed that 85% of reported extravasation events occurred when vasopressors were infused by a catheter that was located distal to the antecubital fossa (389). The occurrence of local tissue injury may be more likely with prolonged administration of vasopressors. Administration of vasopressors for a short period of time (<6 hours) in a well-placed peripheral catheter proximal to the antecubital fossa is unlikely to cause local tissue injury (389).

The time to initiation of vasopressors may be shorter if peripheral access is used. A post-hoc analysis of the ARISE trial showed that 42% of patients had vasopressors initiated via a peripheral catheter with a shorter time to initiation of vasopressors (2.4 [1.3-3.9] vs. 4.9 hours [3.5-6.6], p<0.001) (385). Moreover, most patients who had vasopressors started peripherally achieved a MAP >65 mmHg within 1 hour. Delay in vasopressor initiation and achieving MAP of 65 is associated with increased mortality (390, 391).

Given the low complication rate of peripheral vasopressors and the possibility of restoring blood pressure faster, the benefits of initiating vasopressors for a short period of time in a vein proximal to the antecubital fossa probably outweigh the risks. Therefore, we issued a weak recommendation in favor of the rapid initiation of vasopressors peripherally. If the infusion of vasopressors is still needed after a short period of time, as soon as practical and if resources are available, they should be infused through a central venous access to minimize the risk of complications. The lack of availability and expertise in placement of central venous catheters in different settings is an important consideration (55). Though data are generally sparse on the latter, a study of mostly senior resident doctors in Nigeria concluded that knowledge of central venous catheter placement was limited (392). Though the panel suggests peripheral administration of norepinephrine as a temporizing measure until a central venous catheter can be placed, its longer-term central administration may not be possible in some settings. Larger prospective studies are needed to provide better evidence on the adequacy and safety of peripheral lines in this scenario.

## Fluid balance

|  |
| --- |
| Recommendation |
| 1. There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation.   Remarks  Fluid resuscitation should be given only if patients present with signs of hypoperfusion. |

**Rationale**

The current literature does not provide clear guidance about the best fluid strategy following the initial resuscitation bolus of fluids. The four largest clinical trials in sepsis resuscitation used moderate to large amounts of fluids in the first 72 hours. Although Rivers (393) administered over 13 liters of fluids, ProCESS(64), ARISE (65) and ProMISe (66) administered approximately 7 to 8 L in the usual care groups with a reported low mortality rate. However, recent evidence suggests that IV fluids used to restore organ perfusion may damage vascular integrity and lead to organ dysfunction (394). Data from observational studies have shown an association of high-volume fluid resuscitation and increased mortality, but these studies are likely affected by unmeasured variables (i.e., the administration of higher amounts of fluids to sicker patients) (395, 396). Recent data emerging from Africa showed that higher volume fluid resuscitation in adults was associated with increased mortality, but the generalizability of these data is limited due to the high prevalence of HIV/AIDS and malnutrition in the patients enrolled and the resource-scarce conditions with limited access to ICUs (69).

The current evidence evaluating a restrictive IV fluid strategy in the management of septic patients varies with respect to the inclusion criteria, the definition of restrictive and liberal fluid strategies, the criteria guiding the administration of additional IV fluids (e.g., perfusion parameters vs. hemodynamic variables), and the duration of the interventions (397-401). Moreover, the primary outcomes were mostly related to IV fluid volumes administered during the study period and given the small sample sizes, they were not powered to identify differences in patient-centered outcomes. The ongoing Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial and the Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial will shed some light to this matter (402, 403). Given the quality of the evidence and the variability among existing studies, the panel issued no recommendation for either restrictive or liberal fluid management in the first 24 hours of resuscitation after the initial fluid bolus in patients with sepsis and septic shock. However, it is important to emphasize this discussion does not affect the recommendation for the initial IV fluid bolus and that the administration of IV fluids after the initial fluid bolus should be guided by perfusion parameters and not only by a response in hemodynamic variables.

# VENTILATION

## Oxygen targets

|  |
| --- |
| Recommendations |
| 1. There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure. |

**Rationale**

Patients who are undergoing mechanical ventilation in the ICU often receive a high fraction of inspired oxygen and have a high arterial oxygen tension. The conservative use of oxygen may reduce oxygen exposure and diminish lung and systemic oxidative injury. The evidence for the use of conservative oxygen targets (generally defined as PaO2 55 to 70 mmHg; SpO2 88 to 92%) and therapy in patients with sepsis is limited, with three randomized trials in the critically ill population (404-406). In the 1000-participant ICU-ROX trial (405), conservative oxygen therapy did not significantly affect the primary outcome, which was the number of ventilator-free days, compared with liberal oxygen therapy for ventilated adults in ICU. Mortality at 90 and 180 days did not differ. These findings are at variance with the results of a previous single-center trial, which was stopped early after an unplanned interim analysis. In that trial, conservative oxygen therapy in the ICU was associated with a markedly lower rate of death than usual oxygen therapy (404). In a recent systematic review and meta-analysis of multiple clinical syndromes, investigators found that a conservative oxygen strategy was associated with a lower rate of death in acutely ill adults than a liberal oxygen strategy (407). However, in a post hoc analysis of the ICU-ROX trial including adults with sepsis, point estimates for the treatment effect of conservative oxygen therapy on 90-day mortality raise the possibility of clinically important harm (408).  The LOCO-2 study was terminated early by the data safety and monitoring board and reported no difference in 28 day survival in ARDS patients managed with a conservative oxygenation strategy (409). There are several ongoing trials of conservative oxygen targets that will inform clinical practice in the future. At this point in time, there is insufficient evidence to make an evidence-based recommendation.

## High-flow nasal oxygen therapy

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over non-invasive ventilation.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Acute hypoxemic respiratory failure can result from causes of sepsis such as pneumonia or non-pulmonary infections resulting in ARDS. Patients presenting with hypoxia without hypercapnia are treated with high concentrations of inhaled oxygen which may be delivered conventionally with interfaces including nasal prongs, facemask with reservoir or Venturi mask.

Advanced interventions for patients with severe hypoxia requiring escalation of support include non-invasive ventilation (NIV) or high flow oxygen. Both therapies avoid the complications of intubation and invasive mechanical ventilation and promote patient interaction. In addition to improving gas exchange, NIV may help to reduce work of breathing in select patients. However, NIV use can be associated with development of complications including increased risk of gastric insufflation and aspiration, facial skin breakdown, excessively high tidal volumes as well as patient discomfort related to inability to eat or effectively phonate during therapy.

High flow nasal cannula (HFNC) is a non-invasive, high concentration oxygen delivery interface that confers warming and humidification of secretions, high flow rates to better match patient demand, washout of nasopharyngeal dead space, and modest positive airway pressure effect. The single inspiratory limb of HFNC allows for airflows as high as 60 liters per minute to achieve inspired oxygen fractions (FiO2) as high as 95–100%. However, HFNC is less effective at reducing work of breathing and supplying a moderate or higher level of PEEP (410). Complications with HFNC are possible; however, they are usually self-limited and do not require discontinuing therapy.

When comparing the strategies of NIV versus HFNC for acute hypoxemic respiratory failure *despite conventional oxygen*, a single, large randomized trial has been conducted for direct comparison (411). Although the primary outcome of intubation rate at 28 days was not different, this study demonstrated improved 90-day survival with HFNC compared with NIV (OR 0.42; 95% CI 0.21 to 0.85) and HFNC patients experienced significantly more days free of mechanical ventilation during a 28-day study period (411). In a post hoc analysis of patients with severe hypoxemia (PaO2/FiO2 ≤200 mmHg) from the above trial, HFNC resulted in lower intubation rates compared with NIV (35 versus 58 percent, respectively). A systematic review and meta-analysis of nine RCTs (2,093 patients) showed that HFNC reduces intubation compared with conventional oxygen (RR 0.85; 95% CI 0.74 to 0.99) but does not affect the risk of death or ICU length of stay (412-414). However, the NIV technique was not standardized and the experience of the centers varied.

Although the quality of evidence is low, the benefits of a trial of HFNC for the sepsis patient with non-hypercapnic progressive hypoxia over NIV seems justified. Patients requiring HFNC for acute hypoxemic respiratory failure are at high risk of requiring intubation; therefore, such trials must be accompanied by careful surveillance for ventilatory failure.

## Non-invasive ventilation

|  |
| --- |
| Recommendations |
| 1. There is insufficient evidence to make a recommendation on the use of non-invasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure. |

**Rationale**

When directly compared to invasive positive pressure ventilation, NIV may be able to achieve similar physiologic benefits including improved gas exchange and reduced work of breathing in select patients, while avoiding complications associated with intubation, invasive ventilation, and accompanying sedation. In contrast, NIV can cause mask-related discomfort, unrecognized patient-ventilator asynchrony due to leaks, and gastric insufflation. The main risk of NIV for the indication of acute respiratory failure is the potential for delaying needed intubation and increasing the risk of an interval aspiration events. Studies have suggested that NIV failure is an independent risk factor for mortality specifically in this population, although careful patient selection may reduce this risk (415, 416)

Patients with sepsis-induced hypoxemic respiratory failure may or may not have a competing chronic respiratory disease (ex. COPD, obesity) and the use of NIV for the rescue of patients with exclusively acute hypoxic respiratory failure (“de novo respiratory failure”) is less well studied, but not uncommon. For example, the LUNG SAFE trial demonstrated that NIV was used in 15% of patients with ARDS with varying failure and mortality rates, depending on ARDS severity (417).

A few small RCTs have shown benefit with NIV for early or mild ARDS or de novo hypoxic respiratory failure (418, 419). Since the last guideline distribution, only one additional study was added for analysis (420). Due to small number of patients studied, low quality of evidence, uncertainty regarding whether clinicians can identify hypoxic patients in respiratory failure in whom NIV might be beneficial, and observational data that suggest the potential for harm with NIV in this setting, no clear recommendation can be made. If NIV is used for patients with sepsis-associated hypoxic respiratory failure, we suggest monitoring for an early reduction in work of breathing and close monitoring of tidal volumes (421).

## Protective ventilation in acute respiratory distress syndrome (ARDS)

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis-induced ARDS, we recommend using a low tidal volume ventilation strategy (6 mL/kg), over a high tidal volume strategy (>10 mL/kg).   *Strong recommendation, high quality of evidence.* |

**Rationale**

This recommendation is the same as that of the previous guidelines. Of note, the studies that guide the recommendations in this section enrolled patients using criteria from the American-European Consensus Criteria Definition for Acute Lung Injury and ARDS (422). For the current document, we used the 2012 Berlin definition and the terms mild, moderate, and severe ARDS (PaO2/FiO2 ≤ 300, ≤ 200, and ≤ 100 mm Hg, respectively) (423). Several multicenter RCTs have been performed in patients with established ARDS to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume (424-427). These studies showed differing results, which may have been caused by differences in airway pressures in the treatment and control groups (423, 424, 428).

Several meta-analyses suggest decreased mortality in patients with a pressure- and volume-limited strategy for established ARDS (353, 354). The largest trial of a volume- and pressure-limited strategy showed 9% absolute decrease in mortality in ARDS patients ventilated with tidal volumes of 6 mL/kg compared with 12 mL/ kg predicted body weight (PBW), and aiming for plateau pressure ≤ 30 cm H2O (424).

The use of lung-protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted; however, the precise tidal volume for an individual ARDS patient requires adjustment for factors such as the plateau pressure, the selected positive end-expiratory pressure (PEEP), thoracoabdominal compliance, and the patient’s breathing effort. Patients with profound metabolic acidosis, high minute ventilation, or short stature may require additional manipulation of tidal volumes. Some clinicians believe it may be safe to ventilate with tidal volumes > 6 mL/kg PBW as long as plateau pressure can be maintained ≤ 30 cm H2O (429, 430). The plateau pressure is only truly valuable if the patient is passive during the inspiratory hold. Conversely, patients with very stiff chest/ abdominal walls and high pleural pressures may tolerate plateau pressures > 30 cm H2O because transpulmonary pressures will be lower. A retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cm H2O (431) because lower plateau pressures were associated with reduced hospital mortality (432). A recent patient-level mediation analysis suggested that a tidal volume that results in a driving pressure (plateau pressure minus set PEEP) below 12–15 cm H2O may be advantageous in patients without spontaneous breathing efforts (433). Prospective validation of tidal volume titration by driving pressure is needed before this approach can be recommended. Tidal volumes >6cc/kg coupled with plateau pressures > 30 cm H2O should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1 to 2 hours from its initial value toward the goal of a “low” tidal volume (≈6 mL/kg PBW) achieved in conjunction with an end-inspiratory plateau pressure ≤ 30 cm H2O. If plateau pressure remains > 30 cm H2O after reduction of tidal volume to 6 mL/kg PBW, tidal volume may be further reduced to as low as 4 mL/kg PBW. The clinician should keep in mind that very low tidal volumes may result in significant patient-ventilatoy dyscynchrony and patient discomfort. Respiratory rate should be increased to a maximum of 35 breaths/minute during tidal volume reduction to maintain minute ventilation. Volume- and pressure-limited ventilation may lead to hypercapnia even with these maximum tolerated set respiratory rates; this appears to be tolerated and safe in the absence of contraindications (e.g., high intracranial pressure, sickle cell crisis). No single mode of ventilation (pressure control, volume control) has consistently been shown to be advantageous when compared with any other that respects the same principles of lung protection.

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis-induced severe ARDS, we recommend using an upper limit goal for plateau pressures of 30 cm H2O, over higher plateau pressures   *Strong recommendation, moderate quality of evidence.* |

**Rationale**

This recommendation is unchanged from the previous guidelines, as no new trials evaluating plateau pressure have been published since then. Of note, the 3 RCTs that guide this recommendation (424, 426, 427) enrolled patients using the criteria from the American-European Consensus Criteria Definition for Acute Lung Injury and ARDS (422) whereas the current document use the 2012 Berlin definition and the terms mild, moderate, and severe ARDS (Pao2/Fio2 ≤ 300, ≤ 200, and ≤ 100 mm Hg, respectively) (423). These 3 RCTS compared a strategy of low tidal volume and limited plateau pressure with a strategy using higher tidal volume and plateau pressure; pooled data suggest reduced mortality (RR 0.83; 95% CI 0.70 to 0.97) and more ventilator free days (MD 1.8 days; 95% CI, 0.35 to 3.25) in patients managed with low plateau pressures.

A recent systematic review which included 5 RCTs also identified a strong relationship between plateau pressure and mortality (434). The recommendation is also supported by observational data. LUNGSAFE, a large international observational study, which reported that plateau pressure correlated with mortality; however, the relationship between the two was not evident when plateau pressure was below 20 cmH2O (435). A secondary analysis of 5 observational studies identified a plateau pressure cut-off value of 29 cm H2O, above which an ordinal increment was accompanied by an increment of risk of death (436). We therefore recommend that the upper limit goal for plateau pressure should be less than 30 cm H2O.

|  |
| --- |
| Recommendation |
| 1. For adults with moderate to severe sepsis-induced ARDS, we suggest using higher PEEP over lower PEEP.   *Weak recommendation, moderate quality of evidence.* |

**Rationale**

The recommendation is unchanged from 2016. Two RCTs (437, 438) were published since the 2016 Guidelines (12, 13), but we did not include these trials in the meta-analyses because both studies applied recruitment maneuvers to titrate PEEP levels. Our conclusions did not change in a sensitivity analysis which includes these 2 trials.

Applying higher PEEP in patients with ARDS may open lung units to participate in gas exchange and may increase PaO2. We included 3 multicenter RCTs (439-441) and 1 pilot RCT (442), investigating use of higher PEEP versus lower PEEP strategies *in conjunction with low tidal volumes* for the management of patients with ARDS. Among patients with ARDS receiving lower VTs, we did not identify a significant benefit for use of a higher PEEP versus lower PEEP strategy for improving mortality (RR = 0.93; 95% CI, 0.83- 1.03), days on mechanical ventilation (RR =0.00; 95% CI, -1.02- 1.02), or ventilator-free days (RR =1.48; 95% CI, 0.19-2.76); and there was no increase in the risk of barotrauma (RR =1.49; 95% CI, 0.99-2.23).

A patient-level meta-analysis showed no benefit of higher PEEP in *all patients* with ARDS; however, patients with moderate or severe ARDS (PaO2/FiO2 ≤ 200 mmHg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not (443). A patient-level analysis of two of the randomized PEEP trials (440, 441) suggested that patients with ARDS who respond to increased PEEP with improved oxygenation have a lower risk of death; this association was stronger in patients with more severe ARDS (PaO2/FiO2 < 150 mmHg) compared with patients with less severe ARDS (444).

The optimal method of selecting a higher PEEP level is not clear. One option is to titrate PEEP according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance or lowest driving pressure, reflecting a favourable balance of lung recruitment and overdistension (445). The second option is to titrate PEEP upward while the patient is receiving a tidal volume of 6 mL/kg PBW, until the plateau airway pressure is 28 cm H2O (441). A third option is to use a PEEP/FiO2 titration table that titrates PEEP based on the combination of FiO2 and PEEP required to maintain adequate oxygenation (439-441). A PEEP > 5 cm H2O is usually required to avoid lung collapse (446). Esophageal pressure guided PEEP titration has been evaluated in 2 trials (447, 448). While the pilot study suggested benefit (448), the subsequent 200 patient multicenter RCT that compared PEEP titration guided by esophageal (PES) measurement versus empirical high PEEP-FiO2 titration, showed no significant difference in a composite outcome of death and days free from mechanical ventilation through day 28 (449).

## Low tidal volume in non-ARDS Respiratory Failure

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis-induced respiratory failure (without ARDS), we suggest using low tidal volume as compared to high tidal volume ventilation.   *Weak recommendation, low quality of evidence.* |

**Rationale:**

Previous versions of SSC guidelines issued a strong recommendation with a moderate quality evidence for using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight), over higher tidal volumes (Vt > 8 mL/kg) in the management of patients with ARDS (12, 13, 226). There is not as strong an evidence base, however, for the patients presenting with acute respiratory failure requiring mechanical ventilation who do not fulfil the criteria for ARDS. A 2015 systematic review and meta-analysis of found a reduction in the risk of a composite endpoint of ARDS or pneumonia during the hospital stay in the low tidal volume ventilation group compared to the high tidal volume ventilation group (RR 0.72; 95% CI 0.52 to 0.98) (450). Our analysis of 3 RCTs (1129 patients) showed no difference in mortality with low Vt ventilation (RR 1.07; 95% CI 0.91 to 1.26), with a trend towards lower risk of developing ARDs (RR 0.59; 95% CI 0.34 to 1.02) (supplementary appendix 4).

There are limited data on ventilation strategies for patients with sepsis-induced respiratory failure who do not meet criteria for ARDS. However, sepsis is an independent risk factor for the development of ARDS, and delays in diagnosing ARDS may result in delayed use of low tidal volumes. We therefore suggest that low tidal volume ventilation be used in all patients with sepsis who are receiving mechanical ventilation in order to avoid underuse or delayed use of this intervention. Furthermore, the use of low tidal volume ventilation avoids the risk of promoting ventilator induced lung injury in septic patients in whom the diagnosis of ARDS has been missed.

## Recruitment Manoeuvres

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis-induced moderate-severe ARDS, we suggest using traditional recruitment maneuvers.   *Weak recommendation, moderate quality of evidence.* |
| 1. When using recruitment maneuvers, we recommend against using incremental PEEP titration/strategy.   *Strong recommendation, moderate quality of evidence.* |

**Rationale:**

Many strategies exist for treating refractory hypoxemia in patients with severe ARDS (451). Temporarily raising transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange (446), but could also over distend aerated lung units leading to ventilator-induced lung injury and transient hypotension. Since the publication of the previous SSC Guidelines, two important RCTs were published both of which utilized a “non-traditional” approach to recruitment maneuvers. Instead of the “traditional” recruitment maneuver which consists of the application of sustained continuous positive airway pressure (e.g., 30-40 cm H2O for 30-40 seconds), both trials conducted lung recruitment with incremental PEEP levels, followed by a decremental PEEP titration according to either best respiratory-system static compliance (452) or oxygen saturation (437). When the incremental PEEP recruitment studies are analyzed separately from studies utilizing traditional recruitment maneuvers, recruitment with incremental PEEP is associated with increased 28-day mortality RR 1.12; 95% CI 1.00-1.25), which justifies the strong recommendation against using incremental PEEP titration for recruitment. Traditional recruitment maneuvers appear to improve 28-day mortality (RR 0.79; 95% CI 0.64-0.96) in patients with ARDS (supplementary appendix 4). Although the effects of recruitment maneuvers improve oxygenation initially, the effects can be transient (453). Selected patients with severe hypoxemia may benefit from recruitment maneuvers in conjunction with higher levels of PEEP, but little evidence supports the routine use in all ARDS patients, so we have focused our recommendations to patients with moderate-to-severe ARDS (453). Any patient receiving recruitment maneuvers should be monitored closely and recruitment maneuvers should be discontinued if deterioration in clinical status is observed.

## Prone Ventilation

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis-induced moderate-severe ARDS, we recommend using prone ventilation for greater than 12 hours daily.   *Strong recommendation, moderate quality of evidence.* |

**Rationale:**

There were no new randomized, controlled trials evaluating the use of prone ventilation in sepsis induced severe ARDS published since the 2016 guidelines. Therefore, no change in the recommendation was made. In 2017, a meta-analysis was published (454) that was updated from a previous meta-analysis published in 2010 (455), to which only 1 study, the PROSEVA trial, published in 2013 (456) was added. This repeat meta-analysis confirmed the results from the previous published work: In patients with ARDS and a PaO2/FiO2 ratio <200, the use of prone compared with supine position within the first 36 hours of intubation, when performed for > 12 hours a day, showed improved survival. Meta-analysis including this study demonstrated reduced mortality in severe ARDS patients treated with prone compared with supine position (RR 0.74; 95%CI 0.56-.99) as well as improved oxygenation as measured by change in PaO2/FiO2 ratio (median 23.5 higher; 95%CI 12.4 – 34.5 higher) (454). Most patients respond to the prone position with improved oxygenation and may also have improved lung compliance (457-459). While prone position may be associated with potentially life-threatening complications including accidental removal of the endotracheal tube, this was not evident in pooled analysis (RR 1.09; 95%CI 0.85-1.39). However, prone position was associated with an increase in pressure sores (RR 1.22; 95%CI 1.05-1.41) (460, 461), and some patients have contraindications to the prone position (460, 461).

## Neuromuscular blocking agents

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis induced moderate-severe ARDS, we suggest using intermittent NMBA boluses, over NMBA continuous infusion.   *Weak recommendation, moderate quality of evidence.* |

**Rationale**

The most common indication for neuromuscular blocking agents (NMBAs) use in the ICU is to facilitate mechanical ventilation (462). These drugs may improve chest wall compliance, prevent respiratory dysynchrony, and reduce peak airway pressures (463). In addition, use of NMBA may reduce oxygen consumption by decreasing the work of breathing (464). In the SSC 2016 guidelines, we issued a weak recommendation for using NMBA infusion for 48 hours in sepsis-induced moderate to severe ARDS (12, 13). This recommendation was based on a meta-analysis of 3 trials that examined the role of NMBAs in ARDS (465-467), showing reduced risks of death (RR 0.72; 95% CI 0.58-0.91) and barotrauma (RR 0.43; 95% CI 0.20-0.90) with the use of cisatracurium infusion (468).

Since then, several RCTs have been published (469-471), the largest of which is the ROSE Trial (471). Due to the presence of significant statistical and clinical heterogeneity, a meta-analysis of all 7 trials was not appropriate. A continuous NMBA infusion did not improve mortality when compared to a light sedation strategy with as needed NMBA boluses but no continuous infusion (RR 0.99; 95% CI 0.86 - 1.15). On the other hand, continuous NMBA infusion reduced mortality when compared to deep sedation with as needed NMBA boluses (RR 0.71; 95% CI 0.57 - 0.89). Overall, continuous NMBA infusion reduced the risk of barotrauma (RR 0.55; 95% CI 0.35 - 0.85), but the effect on ventilator-free days, duration of mechanical ventilation, and ICU-acquired weakness was unclear (472, 473).

Given the uncertainty that still exists pertaining to these important outcomes and the balance between benefits and potential harms, the panel issued a weak recommendation favoring intermittent NMBA boluses over a continuous infusion. Importantly, if NMBAs are used, clinicians must ensure adequate patient sedation and analgesia (191, 474). Recently updated clinical practice guidelines are also available for specific guidance (472).

## Extracorporeal membrane oxygenation (ECMO)

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis-induced severe ARDS, we suggest using Veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use.   *Weak recommendation, low quality of evidence.* |

**Rationale:**

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is used in patients with severe acute respiratory failure to facilitate gas exchange in the setting of refractory hypoxaemia or hypercapnic respiratory acidosis (475). It may also be used to facilitate a reduction in the intensity of mechanical ventilation. The evidence for the use of VV-ECMO in sepsis-induced ARDS is limited, with two RCTs completed in the last 10 years to assess the potential efficacy of VV ECMO for severe ARDS (476, 477). The inclusion criteria of the trials were strict and focused on a very sick population of patients with severe ARDS refractory to conventional ventilation strategies and other rescue therapies such as prone position. The evidence in this guideline was downgraded to very low quality due to indirectness.

There were methodological limitations of the included studies. In one trial, all intervention participants were treated at one centre, which may have inflated the effect size because the centre specialized in ECMO management (477). Additionally, some of the participants in this trial did not receive the intervention (477). However, one recent systematic review found that VV ECMO delivered at expert centres reduced mortality for patients with severe ARDS (475). In clinical practice, patient selection is important and usually discussed prior to initiation of ECMO at an ECMO centre. Cost and equity are substantial issues; and registry data will be very important to document longer term outcomes in these patients outside of the clinical trial context.

# ADDITIONAL THERAPIES

## Corticosteroids

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids.   *Weak recommendation; moderate quality of evidence.*  Remarks  The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200mg/day given as 50mg intravenously every 6 hours or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least four hours after initiation. |

**Rationale**

In the 2016 guidance, the accumulated evidence did not support a recommendation for their use if adequate fluid resuscitation and vasopressor therapy were able to restore hemodynamic stability (12, 13) Since then, three large RCTs have been published (478-480). An updated meta-analysis (481) found systemic corticosteroid to accelerate resolution of shock (MD 1.52 days; 95% CI 1.71 to 1.32). A meta-analysis conducted for this guideline revision (supplementary appendix) found an increase vasopressor-free days (MD 1.5 days; 95% CI 0.8 to 3.11 days); however, corticosteroid use increased neuromuscular weakness (RR 1.21; 95% CI 1.01 to 1.45), without a clear effect on short- or long-term mortality.

The overall quality of evidence was moderate. The panel judged the desirable effects (shock resolution, vasopressor free days) to outweigh the undesirable effects of low dose corticosteroid. This observation, when taken into consideration with the resources required, cost of the intervention, and feasibility supported a weak recommendation in favor of using low dose corticosteroid therapy in septic shock.

The optimal dose, timing of initiation, and duration of corticosteroids remain uncertain; recent RCTs used 200 mg per day of IV hydrocortisone in divided doses (479, 480). The three trials (478-480) also used different inclusion criteria: in ADRENAL (480) eligible patients were those on any dose of vasopressor or inotrope for ≥ 4 hours to maintain a MAP > 60 mmHg, and present at the time of randomization. In APROCCHSS (478) the dose of vasopressor was ≥ 0.25µg/kg/min or ≥1mg/hr of norepinephrine or epinephrine, or any other vasopressor for at least 6 hours to maintain a MAP ≥ 65 mmHg. In the ADRENAL (480) study, hydrocortisone was administered for a maximum of seven days or until ICU discharge or death; in APROCCHSS (478) hydrocortisone was administered for seven days; in VANISH (479) 200mg of hydrocortisone was administered daily for 5 days and then tapered over further 6 days.

Our recommendation focuses on adults with septic shock and ongoing requirement for vasopressor therapy. We defined ongoing requirement as a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min for at least four hours after initiation to maintain the target MAP. The dose of hydrocortisone is typically 200mg/day. No dose response benefit was seen in a prior systematic review and meta-analysis (481).

## Blood Purification

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we suggest against using polymyxin B hemoperfusion.   *Weak recommendation; low quality of evidence.* |
| 1. There is insufficient evidence to make a recommendation on the use of other blood purification techniques. |

**Rationale**

Hemoperfusion refers to the circulation of blood through an extracorporeal circuit that contains an adsorbent containing cartridge. The previous guidelines made no recommendation regarding the use of blood purification techniques (12, 13). The updated literature search for guideline identified one new relevant RCT (482)

The most widely investigated technique involves the use of polymyxin B-immobilized polystyrene-derived fibers. Randomized trials of this technique have been previously summarized in a systematic review and meta-analysis (483). An updated meta-analysis of all available RCTs (supplementary appendix) demonstrated a possible reduction in mortality (RR 0.87; 95%CI 0.77 to 0.98, low quality), however this finding was challenged by sensitivity analyses: after excluding high risk of bias trials the risk ratio is 1.14 (95% CI 0.96 to 1.36); and after excluding trials published prior to 2010 we observed higher mortality with hemoperfusion (RR 1.23; 95% CI 1.04 to1.46). Overall, the quality of evidence is judged as low (supplementary appendix).

Substantial uncertainty as to any beneficial effect exists and the frequency of undesirable effects is reported in few trials. Polymyxin B hemoperfusion is expensive, resource intensive, potentially reduces health equity, and is infeasible in low-income economies. All considered, the panel issued a weak recommendation against the use of polymyxin B hemoperfusion therapy.

We did not identify new evidence on other modalities such as hemofiltration, combined hemoperfusion and hemofiltration or plasma exchange. Accordingly, no recommendation regarding the use of these modalities is made. This is unchanged from the 2016 guidelines. Since the analysis new data has emerged, but at this stage was not sufficient for us to re-consider the recommendation (484).

Further research is needed to determine the effect of various blood purification techniques on patient outcomes.

## Red Blood Cell (RBC) Transfusion Targets

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend using a restrictive (over liberal) transfusion strategy.   *Strong recommendation; moderate quality of evidence.*  Remarks  A restrictive transfusion strategy typically includes a hemoglobin concentration transfusion trigger of 70g/L; however, RBC transfusion should not be guided by hemoglobin concentration alone. Assessment of a patient’s overall clinical status and consideration of extenuating circumstances such as acute myocardial ischemia, severe hypoxemia or acute hemorrhage is required. |

**Rationale**

The previous guidance was informed by two RCTs (485, 486). The Transfusion Requirements in Septic Shock (TRISS) trial addressed a transfusion threshold of 70 g/L versus 90 g/L in 1,000 septic shock patients after admission to the ICU. The results showed similar 90-day mortality, ischemic events, and use of life support in the two treatment groups with fewer transfusions in the lower-threshold group. The Transfusion requirements in in Critical Care trial (TRICC), which compared a restrictive transfusion threshold of 70g/L versus 100 g/L in 838 euvolemic ICU patients, demonstrated no difference in the primary outcome (30-day mortality). In the subgroup of 218 patients with sepsis or septic shock 30-day mortality was similar in the two groups (22.8% in the restrictive group vs. 29.7% in the liberal group, p=0.36).

Our literature search identified a recent systematic review and meta-analysis of RCTs (487) and one new RCT: The Transfusion Requirements in Critically Ill Oncologic Patients (TRICOP) trial (488). This trial randomized 300 adult cancer patients with septic shock to either a liberal (hemoglobin threshold, < 90 g/L) or restrictive strategy (hemoglobin threshold, < 70 g/L) of RBC transfusion. At 28 days after randomization, the mortality rate in the liberal group was 45% (67 patients) versus 56% (84 patients) in the restrictive group (HR 0.74; 95% CI 0.53-1.04; p = 0.08) with no differences in ICU and hospital length of stay. At 90 days after randomization, mortality rate in the liberal group was lower (59% vs 70%) than in the restrictive group (hazard ratio, 0.72; 95% CI 0.53-0.97).

Our update of the meta-analysis showed no difference in 28-day mortality (OR 0.99 95% CI 0.67-1.46, moderate quality). This is due to the inclusion of the TRICOP study where lower 28 mortality was observed with a liberal strategy. Overall, the quality of evidence was judged moderate.

The overall balance of effects is uncertain and does not favor either the intervention or comparator. However, a restrictive strategy was determined likely beneficial with regards to resources required, cost effectiveness, and health equity considerations. A restrictive strategy is feasible in low- and middle-income countries. The 2016 strong recommendation favoring a restrictive strategy is unchanged; however, the overall quality of evidence changed from strong to moderate.

## Immunoglobulins

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we suggest against using intravenous immunoglobulins   *Weak recommendation, low quality of evidence.* |

**Rationale**

Patients with sepsis and septic shock may have evidence of hyper-inflammation and immunosuppression (489). There are no high-quality studies examining the effect of intravenous (IV) immunoglobulins on the outcomes of patients with sepsis or septic shock. The previous guidance was a weak recommendation against their use (12, 13).

Our literature search identified two new RCTs (490, 491) and three meta-analyses (350, 492, 493) evaluating the effects of polyclonal IV immunoglobulins (IVIG) and immunoglobulin M-enriched polyclonal Ig (IVIGM) in patients with sepsis. The updated meta-analyses demonstrated reduced mortality with IVIG (RR 0.73; 95% CI 0.51 to 0.91) and IVIGM (RR 0.69; 95% CI 0.55 to 0.85), however the quality of evidence is low with many of the included studies at high risks of bias including single-center trials with small sample size, undefined randomization, allocation and blinding procedures, different dosing regimens and durations of treatment, different controls and few studies reported adverse events. Furthermore, after excluding high risk of bias studies, the significant reduction in mortality is no longer apparent.

Overall, the balance of effects (beneficial and undesirable) remains uncertain. Intravenous immunoglobulin is also relatively expensive, possibly not cost-effective and may reduce health equity. Its cost also limits its feasibility in countries with low- and middle-income economies. Based on these judgements, clinicians may consider avoiding the routine use of IV immunoglobulins in patients with sepsis and septic shock. Large, multi-center, well designed, RCTs are needed to resolve the uncertainty regarding the role of immunoglobulin therapies in this patient population.

## Stress Ulcer Prophylaxis

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we suggest using stress ulcer prophylaxis.   *Weak recommendation, moderate quality of evidence.* |

**Rationale**

Stress ulcers develop in the gastrointestinal (GI) tract of critically ill patients and can be associated with significant morbidity and mortality (494). In 2016, this guideline recommended stress ulcer prophylaxis for patients with risk factors (12, 13).

Our literature search identified one new RCT (495) and the meta-analysis from the previous guideline was updated. This demonstrated no effect on mortality (RR 1.01 95% CI 0.93-1.10) and a reduction in GI hemorrhage (RR 0.52 95% CI 0.45-0.61). A sensitivity analysis including only trials at low risk of bias provided similar results. No increase in *Clostridoides difficile* colitis or pneumonia was observed. (However, it was noted that the most recent (and largest) RCT did not demonstrate any effect of pantoprazole versus placebo on 90-day mortality and a composite outcome of clinically important events (495). A recent meta-analysis published since the finalization of the literature searches has suggested that there is a higher risk of recurrent *Clostridoides difficile* infections withproton pump inhibitors (496).

Overall, it was judged that the evidence probably favored the administration of stress ulcer prophylaxis. This is driven by a modest reduction in gastrointestinal hemorrhage for which there is moderate quality of evidence (supplementary appendix). While no adverse effects were observed, the quality of evidence for these outcomes was low. Stress ulcer prophylaxis is relatively inexpensive, requires limited resources and is applicable to countries with low-income economies. These judgements support a weak recommendation for the use of stress ulcer prophylaxis in at-risk patients. This represents a downgrading of the strong recommendation based on low quality evidence made in 2016.

A recent systematic review evaluated risk factors for clinically important GI bleeding (497). After excluding high risk of bias studies, risk factors included: coagulopathy (relative effect (RE) 4.76; 95% CI 2.62-8.63), shock (RE 2.60; 95% CI 1.25-5.42), and chronic liver disease (RE 7.64; 95% CI 3.32-17.58). The effect of mechanical ventilation on clinically important bleeding was unclear (RE 1.93, 0.57-6.50, very low certainty).

## Venous Thromboembolism (VTE) Prophylaxis

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend using pharmacologic VTE prophylaxis unless a contraindication to such therapy exists.   *Strong recommendation, moderate quality of evidence.* |
| 1. For adults with sepsis or septic shock, we recommend using low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prophylaxis.   *Strong recommendation, moderate quality of evidence.* |
| 1. For adults with sepsis or septic shock, we suggest against using mechanical VTE prophylaxis in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Critically ill patients are at risk for deep vein thrombosis (DVT) as well as pulmonary embolism (PE). The incidence of DVT acquired in the ICU may be as high as 10% (498), the incidence of acquired PE may be 2%–4% (499, 500).

No new RCT evidence was identified. Our previous meta-analysis demonstrated a significant reduction in both DVT and PE and no increase in bleeding complications.

On balance, the effect favors the intervention with a moderate quality of evidence. The cost of intervention is not large, and it is likely feasible in countries with low- and middle-income economies. These judgements support a recommendation for the use of pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication exists. The recommendation is unchanged from the 2016 guidelines.

Our literature review found no new RCT evidence comparing the administration of low molecular weight heparin (LMWH) to unfractionated heparin (UFH). The prior meta-analysis demonstrated significantly lower rates of DVT following the administration of LMWH compared to UFH (RR 0.84 95% CI 0.71-0.98). No difference in the rates of clinically significant bleeding, mortality or PE were observed. The overall quality of evidence was rated as moderate: it was downgraded for imprecision. It was determined that the balance of overall effects favored LMWH over UFH. Any difference in resources required between the two interventions was considered to be negligible, and LMWH administration was feasible and applicable in countries with low- and middle-income economies. Further, LMWH may have greater consumer acceptance as it requires only one subcutaneous injection daily. These judgements support a recommendation for the use of LMWH over UFH for VTE prophylaxis in patients with sepsis or septic shock. This recommendation is unchanged from the 2016 guidelines.

Combined pharmacologic prophylaxis and mechanical prophylaxis with intermittent pneumatic compression (IPC) and/or graduated stockings may offer another option for patients with sepsis and septic shock. In the 2016 guidelines, a suggestion to use combination therapy whenever possible, was based on indirect and imprecise data (12, 13). Our literature search identified one new RCT that compared the combination of mechanical and pharmacological prophylaxis to pharmacological prophylaxis alone (501).

The PREVENT study randomized 2003 critically ill patients to intermittent pneumatic calf compression alone or in combination with pharmacological prophylaxis (501). No difference in mortality (RR 0.98 95% CI 0.84-1.13), or the rates of DVT and PE were observed. No difference in lower extremity ischemia was demonstrated. The study was downgraded during the quality assessment for imprecision. For the outcome of mortality, the quality was assessed as moderate; for other outcomes it was further downgraded for risk of bias.

It was judged that any effects of the intervention (mechanical prophylaxis in addition to pharmacologic), either beneficial or undesirable, were likely trivial (supplementary appendix). However, there are resource implications and costs associated with the use of mechanical VTE prophylaxis. These, together with the lack of any effect on a patient centered outcome support a weak recommendation against the use of the combination of mechanical and pharmacologic prophylaxis.

It is acknowledged that in some patents with sepsis and septic shock pharmacologic prophylaxis may be contraindicated. These patients may benefit from mechanical VTE prophylaxis. No data for this population exist. Further research is indicated.

## Renal Replacement therapy

|  |
| --- |
| Recommendations |
| 1. In adults with sepsis or septic shock and AKI who require renal replacement therapy, we suggest using either continuous or intermittent renal replacement therapy.   *Weak recommendation, low quality of evidence.* |
| 1. In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we suggest against using renal replacement therapy.   *Weak recommendation, moderate quality of evidence.* |

**Rationale**

Two systematic reviews and meta-analyses (502, 503) summarized the total body of evidence: they do not show a difference in mortality between patients who receive continuous (CRRT) versus intermittent hemodialysis (IHD). The results remained the same when the analysis is restricted to RCTs (503).

Our updated literature search identified no new RCTs but two meta-analysis comparing continuous and intermittent renal replacement therapies (504, 505). The quality of evidence was judged as low. The balance of effects favored neither (IHD) nor CRRT. It was acknowledged that the resources required for the interventions vary. In low- and middle-income economies, the specialized equipment, expertise and personal required for continuous modalities may not be available. The recommendation, for either intervention, is unchanged from the 2016 guidelines

Timing of renal replacement therapy initiation is of importance. Prior research has suggested benefit (506) or harm (507)for “early” versus “delayed” initiation of RRT.

Our search identified a new RCT comparing early versus delayed RRT (508).This trial included 488 patients with AKI and septic shock. It was stopped early, after the second planned interim analysis, for futility. Eligible patients were those with septic shock (within 48 hours of the onset of vasopressor therapy and AKI defined as oliguria (<0.3ml/kg/hr. for ≥24 hours), anuria for 12 hours or more, or a serum creatinine level 3 times baseline accompanied by a rapid increase of ≥ 0.5 mg/dl. Subsequent to the censor date for our literature search, the results of the STARRT-AKI trial were published. The trial, which randomized 3000 participants, demonstrated no difference in mortality in those allocated to an accelerated strategy of RRT compared to those allocated to a “standard” strategy. No differential effect was observed in the a priori sepsis subgroup (1689 patients (509).

The results of this trial were included in an updated meta-analysis (supplementary appendix). No effect of the timing of initiation of renal replacement therapy on mortality and renal recovery was observed. The IDEAL-ICU trial (508) did not report central venous access device (CVAD) infections: the results for this outcome are unchanged from 2016. The certainty of evidence for the key outcomes of mortality, renal recovery and CVAD infection was a least moderate and was only downgraded for imprecision (supplementary appendix). Overall, the balance of effects favored delayed rather than early initiation of RRT. This is principally driven by the higher rate of CVAD infection in the “early” initiation. Therefore, after considering of the resources required, cost and health equity issues, the panel issued a weak recommendation against the use of RRT in patients with sepsis and AKI for increases in creatinine or oliguria alone, and without other absolute indications for dialysis (uremic complications, refractory academia, refractory fluid overload or hyperkalemia).

## Glucose control

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we recommend initiating insulin therapy at a glucose level of ≥ 180mg/dL (10mmol/L).   *Strong recommendation; moderate quality of evidence.*  Remark  Following initiation of an insulin therapy, a typical target blood glucose range is 144-180mg/dL (8-10mmol/L). |

**Rationale**

Hyperglycemia(> 180mg/dL), hypoglycemia and increased glycemic variability are associated with increased mortality in critically ill patients (510-512). The American Diabetes Association, in its most recent recommendations for glycemic control of critically ill patients, recommended the initiation of insulin therapy for persistent hyperglycemia > 180 mg/dL and thereafter a target glucose range of 140–180 mg/dL (513).

In a single center study, targeting blood glucose to 80-110mg/dL reduced ICU mortality (514), however this finding was not reproduced in subsequent multi-center RCTs (515, 516). Meta-analyses also report a higher incidence of hypoglycemia (glucose < 40 mg/dL) in critically patients where blood glucose was targeted to 80-110 mg/dL (517, 518). The previous recommendation, to commence insulin when two consecutive blood glucose levels are > 180mg/dL, derives from the NICE-SUGAR trial (519). A summary of the evidence for this trigger of > 180mg/dL is found in the supplementary appendix. In this version of the guideline, we asked a new question: in adults with sepsis of septic shock, what level of glucose should trigger one to start an insulin infusion (>180 or >150 mg/dl)?

We identified a recent network meta-analysis of 35 RCTs (520). The analysis compared four different blood glucose targets (<110, 110-144, 144-180, and >180 mg/dL). No significant difference in the risk of hospital mortality was observed between the four blood glucose ranges. Target concentrations of <110 and 110–144 mg/dL were associated with a four to nine-fold increase in the risk of hypoglycemia compared with 144–180 and >180 mg/dL. No significant difference in the risk of hypoglycemia comparing a target of 144–180 and >180 mg/dL was demonstrated (OR 1.72; 95% CI 0.79-3.7).

The overall quality of evidence was rated as moderate (Supplementary appendix). Overall, the balance of effects favored initiation of insulin therapy at a glucose level of > 180mg/dl. This was principally driven by the increased risk of hypoglycemia observed with lower targets. No significant differences existed between the two-insulin initiation blood glucose levels evaluated. After considering the resources required, cost, health equity issues, and applicability to low- and middle-income economies, the panel made a strong recommendation for the initiation of insulin therapy at a glucose level of ≥ 180mg/dL (10mmol/L).

Further research is indicated to: (1) identify which technologies including electronic glucose management, continuous glucose monitoring, and closed loop systems, can more safely achieve better glycemic control and lower rates of hypoglycemia; and (2) determine the optimal glycemic control for different patient populations including diabetic and nondiabetic patients, medical and surgical patients.

## Vitamin C

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock, we suggest against using IV vitamin C.   *Weak recommendation, low quality of evidence.* |

**Rationale**

Vitamin C is known to have anti-inflammatory properties (521). In 2017, a single center before and after study reported shorter duration of vasopressor therapy and lower mortality following the administration of combination of high dose vitamin C, hydrocortisone, and thiamine to patients with sepsis and septic shock (522). Our literature review found one systematic review and meta-analysis (523) (containing six RCTs) and one additional RCT (524).

Our updated analysis (supplementary appendix) included seven RCTs (416 critically ill patients). The use of Vitamin C did not reduce mortality compared to usual care (RR 0.79; 95% CI 0.57 to 1.1, low quality). One study reported reduced vasopressor use at 168 hours (524). Of the patients alive at 7 days, 22% (16/72) administered Vitamin C remained on vasopressor therapy compared to 10% (6/59) of controls.

Subsequent to the censor date for our literature search, the results of two additional RCTs of Vitamin C versus placebo were published (525, 526). In the study by Fujii et al (525), 211 adults with septic shock were randomized to the combination of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone. The authors reported no difference for the primary outcome of time alive and free of vasopressors up to 168 hours between the intervention and control group (median 122.1 hours [IQR 76.3-145.4 hours] vs 124.6 hours [IQR 82.1-147 hours]; p=0.83). Ninety-day mortality was 28.6% (30/105) in the vitamin C group, and 24.5% (25/102) in the control group (HR 1.18; 95% CI 0.69 to 2.0). In the study by Moskowitz et al (526), 200 patients were randomized to a combination of Vitamin C, Hydrocortisone and thiamine vs placebo. No difference in the primary outcome of mean SOFA score change at 72 hours post enrolment was observed. At 30 days, 34.7% (35/101) of patients randomized to combination therapy had died vs. 29.3% (29/99) randomized to placebo (HR, 1.3; 95% CI, 0.8-2.2; p=0.26). When these data are added to our meta-analysis, the point estimate for mortality becomes RR 0.9 (95% CI 0.69-1.18: low quality).

The overall size of any desirable effect was judged as small with a low quality of evidence (supplementary appendix). There are limited available data of any undesirable effects: it was noted that the point estimate of the HR for 90-day mortality in the largest RCT (525) was 1.18 (95% CI 0.69-2.00) i.e., favoring the control group. The balance of effects was accordingly judged as favoring neither the intervention nor the comparator. The intervention itself requires limited resources and is feasible in low- and middle-income economies.

The panel issued a weak recommendation against the use of Vitamin C in patients with sepsis and septic shock. The results of additional RCTs are expected to be reported in late 2020: they may influence the quality of evidence and future updates of the guidelines.

## Bicarbonate Therapy

|  |
| --- |
| Recommendations |
| 1. For adults with septic shock and hypoperfusion-induced lactic acidemia, we suggest against using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements.   *Weak recommendation, low quality of evidence.* |
| 1. For adults with septic shock, severe metabolic acidemia (pH ≤ 7.2) and AKI (AKIN score 2 or 3), we suggest using sodium bicarbonate therapy   *Weak recommendation, low quality of evidence.* |

**Rationale**

The previous guidance was based on two small, blinded crossover RCTs that compared equimolar saline vs sodium bicarbonate in patients with lactic acidosis and failed to reveal any difference in hemodynamic variables or vasopressor requirements (527, 528). A weak recommendation was made against the use of bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15.

Our literature search identified one new RCT (529). In this multicenter trial, 400 patients with severe metabolic acidemia (pH ≤ 7.20) were randomly allocated to receive IV 4.2% sodium bicarbonate with the aim of achieving an arterial pH of 7.3, or control (no bicarbonate). No between-group difference was observed in the primary outcome of a composite of 28-day mortality and organ failure at day 7. However, hypernatremia, hypocalcaemia, and metabolic alkalosis were observed more frequently in those randomized to bicarbonate. In the subgroup of patients with AKI defined as AKI Network (AKIN) stage 2 or 3 at randomization (182/389-47%), lower mortality was observed with bicarbonate therapy: control 57/90 (63%), bicarbonate (42/92- 46%), absolute risk reduction (ARR) –17·7% (–33·0 to –2·3), p =0·016. There was a significant differential effect between patients with an AKIN score of 2 or 3 compared with those with a score of 0-1 (p value for heterogeneity = 0.023).

Sepsis was present in 61% (238/389) of patients at the time of randomization. No differential effect was observed between patients with vs without sepsis. The outcomes of patients with both sepsis and AKI were not reported.

Overall, the quality of evidence is low (supplementary appendix). The summary of judgements supported a weak recommendation against the intervention. The 2016 recommendation is essentially unchanged. However, when considering the subset of patients with septic shock, severe metabolic acidosis and AKI, the balance of effects probably favors IV bicarbonate. A weak recommendation for the use of IV bicarbonate in this population was made.

## Nutrition

|  |
| --- |
| Recommendation |
| 1. For adult patients with sepsis or septic shock who can be fed enterally, we suggest early (within 72 hours) initiation of enteral nutrition.   *Weak recommendation, very low quality of evidence.* |

**Rationale**

The early administration of enteral nutrition in patients with sepsis and septic shock has potential physiologic advantages related to the maintenance of gut integrity and prevention of intestinal permeability, dampening of the inflammatory response, and modulation of metabolic responses that may reduce insulin resistance (530, 531). Our literature search defined early enteral nutrition as enteral nutrition commenced within 72 hours of ICU admission. The comparator was enteral nutrition commenced after 72 hours.

The literature search identified one new RCT (532). This multicenter trial conducted in 44 French ICUs randomized 2410 invasively mechanically ventilated patients with shock to early enteral nutrition vs early parenteral nutrition. 1504 (62%) of the participants had sepsis. The results of this trial were included in a meta-analysis with four relevant trials from the 2016 guidelines (533-536). No significant effect favoring early enteral nutrition was observed for all outcomes evaluated. The quality of evidence was assessed low or very low: downgrades were for risk of bias, inconsistency, and imprecision.

The overall balance of effects did not favor either early enteral feeding (within 72 hours) compared with enteral feeding commenced after that time. Although the available evidence is of low quality, it does not suggest harm following the institution of early enteral feeding. Neither intervention was considered more beneficial when considering resources utilization, cost effectiveness, and equity issues. The institution of early enteral nutrition was also considered feasible in low- and middle-income economies.

Given the plausible possibility of benefit when considering the available physiological data, and the absence of any apparent harm, a weak recommendation to start feeding early in patients with sepsis and septic shock was made. Further research addressing this question in patients with sepsis and septic shock is required.

# LONG-TERM OUTCOMES AND GOALS OF CARE

Patients who survive a protracted period of ICU care for sepsis typically face a long and complicated road to recovery. There will not only be physical rehabilitation challenges to overcome but also great uncertainty about the way to organize and coordinate care, both to promote recovery/avoid complications/recurrence and to ensure care is matched to patient and family goals of care.

There is broad consensus that the current healthcare system is likely falling short of what optimal care during the recovery period might look like for this patient population. However, generating a robust evidence base upon which to make concrete recommendations about changes in the care paradigm has proven to be extraordinarily difficult. Some of the difficulties relate to:

* not all patients are the same, and understanding which patients ought to receive which interventions is very poor
* not all healthcare delivery systems are the same – even within one system, some patients may be very well supported while others may not – really complicating what ‘control’ care looks like
* lack of understanding about dosing and intensity of many of the proposed interventions, and when and whether they should be combined in packages is generally missing.

While these issues of patient heterogeneity, variable control care, and lack of understanding about ideal configuration of interventions are protean, they are exquisitely true in this setting: while two ICUs may be different, each ICU discharges patients into a broad and variable milieu of settings. The variation in both ICU and post-ICU management of critically ill patients increases the complexity of understanding and defining best practice.

Thus, putting all this together, there are some overarching conceptual features about ‘best practice’ that the panel endorses, recognizing, however, that the nature, timing, and combination of these broad aspects of care may vary, and strong unambiguous evidence for the ‘how to’ for these things is often going to be lacking.

## Goals of Care

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend discussing goals of care and prognosis with patients and families over no such discussion.   *Best Practice Statement.* |
| 1. For adults with sepsis or septic shock, we suggest addressing goals of care early (within 72 hours) over late (72 hours or later).   *Weak recommendation, low quality evidence.* |
| 1. There is insufficient evidence to make a recommendation for any specific standardized criterion to trigger goals of care discussion. |

**Rationale**

Patients with sepsis or septic shock are at high risk of multi-organ failure, long-term functional sequelae, and death. Some patients may accept any and all treatment for their condition, but others may consider limitations depending on prognosis, invasiveness of interventions, and predicted quality of life (QoL). A discussion of goals of care and prognosis is essential to determine which treatments are acceptable and those interventions that are not desired (537).

No studies were identified that compared discussions of goals of care and prognosis versus no such discussion in critically ill or septic patients. While advance care planning in patients with life-limiting illness may reduce use of life-sustaining treatments, it may also increase use of hospice and palliative care, and improve concordance between treatment and patient values (538). The relevance of advance care planning for future health needs to goals of care discussions at the time of a critical illness is unclear. Despite lack of evidence, the panel recognized that discussion of prognosis and exploration of goals of care with patients and/or family is a necessary precondition to determine patient treatment preferences and providing value-concordant care. Thus, the panel made a best practice recommendation to discuss goals of care and prognosis with patients and families.

The timing of discussions of goals of care and prognosis in the ICU was addressed in one study where 26% of patients had infection or sepsis as a primary diagnosis (539). A multicomponent family support intervention included a meeting at 48 hours after ICU admission that included discussion of goals of care and prognosis. The support intervention did not affect family psychological outcomes but did improve perceived quality of communication and perception of patient- and family-centeredness of care. A reduction in ICU length of stay was noted yet it is unknown if the reduction is due to increased mortality. Based on this study, early (within 72 hours of ICU admission) discussion of goals of care is suggested.

We identified several studies exploring the use of specific criteria to trigger a goals of care discussion in critically ill patients, though none report the proportion of patients with sepsis or septic shock. Conflict over values-based treatment was used to trigger ethics consultation in the intervention group in three randomized ICU studies (540-542). Reductions in ICU and ventilator days in intervention patients who died before hospital discharge were found in 2 studies (540, 541), and the third study found overall shorter ICU and hospital stay in the ethics consultation group (542). Ethics consultation did not affect overall mortality in any study. Duration of mechanical ventilation and duration of ICU stay were used to trigger specific interventions in two randomized studies (543, 544). The study by Carson et al randomized patients after 7 days of mechanical ventilation to a group receiving an informational brochure and 2 family meetings with palliative care specialists to address goals of care or a group receiving an informational brochure and meetings led by the ICU team (544). Palliative care meetings failed to show benefit in decreasing anxiety and depression in surrogate decision makers in the intervention group but did increase post-traumatic stress disorder (PTSD) symptoms. No benefit was demonstrated on family satisfaction, ICU days, or hospital days. Andereck et al randomized patients after 5 days or more in a medical-surgical ICU to proactive ethics consultation versus usual care (543). Ethics consultation did not result in a reduction in ICU stay, hospital stay, or life-sustaining treatments in patients who did not survive to discharge. Neither study demonstrated an effect of interventions on mortality. One study (545) investigated the use of an automated early warning system alert in patients hospitalized on medical units (27% with infection). The early warning system did not impact hospital mortality or hospital length of stay but did reduce ICU transfers and ICU length of stay and increased documentation of advance directives and resuscitation status compared to the usual care group.

Given the variety of triggers used in these studies and the lack of superiority of any single trigger, no recommendation can be made for specific criteria to initiate a goals of care discussion. The timing of and triggers for such discussions should take into account the current condition of the patient, premorbid health and QoL, prognosis, response to treatment, interventions under consideration, anticipated QoL following treatment, availability of resources, and readiness and ability of the patient or family to engage in the discussion.

Public members judged it important to assess patient and family understanding of the information provided in goals of care discussion and for a member of the care team to check with them to determine if further explanations are needed. Additional input included the recommendation that a goals of care discussion should take into account chronic medical conditions in addition to sepsis.

## Palliative Care

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we recommend integrating principles of palliative care (which may include palliative care consultation based on clinician judgement) into the treatment plan, when appropriate, to address patient and family symptoms and suffering.   *Best Practice Statement.* |
| 1. For adults with sepsis or septic shock, we suggest against routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgement.   *Weak recommendation, low quality evidence.* |

**Rationale**

While the goal of treating most patients with sepsis or septic shock is to improve survival, some patients have significant comorbidities that may be life limiting or significantly impair QoL. Palliative (supportive) care may be particularly helpful in patients with sepsis who are not responding to treatment or for whom sepsis is an end-stage manifestation of their underlying chronic illness. Studies have evaluated palliative care interventions in the ICU but not specifically in patients with sepsis (544, 546-549). However, indirect evidence from these studies was judged likely to apply to patients with sepsis.

Criteria for patient inclusion and the interventions in these studies demonstrate significant heterogeneity. Inclusion criteria for ICU patients consisted of mechanical ventilation for 7 days (544), high risk on a palliative care screen (549), physician determination that care should not be escalated or care should be withdrawn (546), physician belief that the patient would die in a few days (548), or death in the ICU or within 30 hours of transfer out of the ICU (547). Interventions comprised formal palliative care consultation (544, 546, 549), a complex quality improvement project to improve end-of-life care (547), and a planned end-of-life conference conducted by intensivists according to specific guidelines along with a bereavement brochure (548).

Various outcome measures are reported but none of the studies evaluated critical patient-centered outcomes such as QoL, physical or cognitive recovery, psychological outcomes, or symptoms. Only one study with a structured palliative care intervention (548) demonstrated a beneficial effect of lower prevalence of anxiety and depression symptoms and PTSD symptoms in family members 90 days after the patient’s death. In contrast, Carson et al. found an increase in PTSD symptoms in family surrogate decision makers with palliative care consultation. (544) Palliative care interventions had no significant impact on family satisfaction with care, ICU length of stay (544, 546-549), hospital length of stay (544, 546, 549), or mortality (544, 546, 549).

Overall evidence for routine formal palliative care interventions in ICU patients is of low quality and provides mixed evidence of benefit. Thus, the panel suggests against routine formal palliative care consultation for all patients with sepsis or septic shock, instead using clinician judgment to determine which patients and families may benefit from a palliative care consultation.

Despite the lack of evidence for formal palliative care consultation, the panel and public members judged that the principles of palliative care, whether instituted by palliative care specialists, intensivists or other clinicians are essential to address symptoms and suffering in patients and their families. Therefore, the panel made a best practice statement recommending incorporation of palliative care principles in the care of patients with sepsis and septic shock.

## Peer support groups

|  |
| --- |
| Recommendations |
| 1. For adult survivors of sepsis or septic shock and their families, we suggest referral to peer support groups over no such referral.   *Weak recommendation, very low quality of evidence.* |

**Rationale**

Peer support groups have been used to enhance recovery from illness when survivors have long-lasting disability but have only recently been used in critical care and sepsis (550-552). With increased recognition of post-intensive care syndrome (PICS) in survivors of critical illness and their families, peer support represents a patient-centered approach to improve long-term outcomes (553, 554). Public members suggested that referral to an individual peer support person during the sepsis hospitalization may provide a means of support and hope for recovery while referring sepsis survivors and their families to a peer support group may help them regain functional and emotional health.

Models of peer support are numerous and include community-based in person or virtual peer support; outpatient ICU follow-up clinics (with or without psychologist support); within-ICU peer support; and individual peer mentors (552). We did not identify sufficient studies to allow for meta-analysis. Four observational studies examined the impact of peer support groups on ICU patients, though they were not specific to sepsis patients. These studies evaluated the impact of peer support in ICU survivors from a surgical ICU (555), two general ICUs (556-558) and two cardiac ICUs (556, 559). Group models varied, with facilitated in-person (555, 558), group-based integrated with rehabilitation (556, 557) or a “buddy” with a former patient-to-patient program (559). In several qualitative studies, ICU survivors described peer support as a helpful aid to recovery (560-564). Three qualitative studies identified two common themes of peer support, 1) benefit of knowing that others shared similar experiences and 2) benefit of shared coping with others (565).

Overall quality of evidence was judged to be very low for the impact of peer support groups on outcomes. No studies described costs associated with support groups, which will vary given the model and resource availability. Research evaluating support groups is needed with at least two RCTs planned (565-567).

Despite the very low certainty of evidence, the panel made a weak recommendation in favor of referring patients and families to peer support, which will increase the equity of access to such services. As individuals who receive referral to peer support have the choice to participate or not (based on personal preference, timing, location, functional status, and resources required,) a weak recommendation provides an opportunity to access support for sepsis survivors who otherwise may not know where to turn (553).

## Transitions of care

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock, we suggest using a handoff process of critically important information at transitions of care, over no such handoff process.   *Weak recommendation, very low-quality evidence.* |
| 1. There is insufficient evidence to make a recommendation for the use of any specific structured handoff tool over usual handoff processes. |

**Rationale**

Transitions of care are prone to communication errors, which have been identified as a barrier to the timely detection and management of sepsis (568). Improving handoff at transitions in care represents an opportunity to improve patient outcomes across the entire spectrum of sepsis care, from hospitalization to return to the community.

We did not identify any studies specifically evaluating patients with sepsis. Structured handoff interventions for critically ill patients have been evaluated at many transitions of patient care (ED/ICU, OR/ICU, ICU/ward, and hospital/home). The majority are observational pre-post studies and report process measures such as completeness and accuracy of communication rather than clinical outcomes. There were insufficient data to allow for meta-analysis.

A single RCT using a stepped-wedge design, in 8 ICUs, evaluated the impact of a standardized handoff process, finding no effect upon duration of mechanical ventilation, ICU length of stay, or duration of handover (569). Observational studies of structured handoff process have demonstrated mixed effects, with some finding reductions in unexpected clinical events, (570) or ICU readmission (571, 572) and others without impact upon length of stay (573), mortality (573, 574) or hospital readmission (573, 574).

Overall quality of evidence was judged to be very low. While it is unclear whether structured handoffs impact important patient outcomes, many sepsis interventions and tests are time-dependent and communication failures may increase the chances of critical medical errors. Structured handoff processes appear to result in more complete and accurate transfer of information, without any undesirable effects. Thus, despite the low certainty of evidence, the panel made a weak recommendation in favor of structured handoff processes at transitions of care. Of the structured handover tools studied, none specifically applies to sepsis. Given the wide variety of hospital staffing models, medical records, and discharge processes, along with the lack of evidence to recommend any one tool over another, the panel chose to make no recommendation for a specific structured handover tool.

## Screening for economic or social support

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock and their families, we recommend screening for economic and social support (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs.   *Best Practice Statement.* |

**Rationale**

Non-medical social needs and potentially modifiable factors such as economic and social support largely influence health outcomes. While survival from sepsis is improving, long-term health requires survivors to have the resources to recover and thrive. Notably, critically ill patients have a decline in socio-economic status (SES) after their illness (575). Many observational studies describe the relationship between various socioeconomic supports and patient outcomes that suggest that low SES, substance abuse and poor nutritional status lead to poor outcomes, and that critical illness itself results in lower SES post-illness. Additionally, living in neighborhoods with low SES is associated with an increased risk of sepsis (576), community-acquired bacteremia (576) and death from bacteremia (577) and worse outcomes (578). Racial disparities in sepsis (579) are at least partially explained by living in medically underserved neighborhoods (580).

Screening for economic and social support may help reduce these inequities. Although socioeconomic screening is considered part of standard clinical practice, all clinical teams in many settings may not do it. This may be particularly true in the critical care setting where patients are often unable to communicate, and social determinants of health may not be addressed during management of the acute illness.

No studies were identified comparing screening versus no screening for economic and social support. Furthermore, it is unlikely that many research studies would be conducted, since locally available social needs and supports vary. In LMIC where resources are limited, needs may be vast. Despite these variations, social and economic screening may identify challenges that sepsis survivors are experiencing, allowing clinicians to identify potential resources and referrals, which can assist to improve long-term health outcomes.

## Sepsis education for patients and families

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock and their families, we suggest offering written and verbal sepsis education (diagnosis, treatment, and post-ICU/post-sepsis syndrome) prior to hospital discharge and in the follow-up setting.   *Weak recommendation, very low-quality evidence.* |

**Rationale**

Almost 40% of sepsis survivors are re-hospitalized within 3 months, often for preventable conditions (581), contributing to increased healthcare costs (582). Given the risk of post-sepsis morbidity, sepsis education may have a role in the timely healthcare seeking behavior in sepsis survivors who experience complications. In an international survey of sepsis survivors from 41 countries, 45% and 63% reported dissatisfaction with sepsis education at the acute and post-acute phase, respectively (583). We identified six RCTs that evaluated educational interventions for critically ill patients and their families (584-589). Only one specifically studied patients with sepsis (589), evaluating a complex intervention, which included education along with primary care follow-up and post-discharge monitoring. Varied education methods were employed, including delivery by trained nurses (587, 589), multimedia nursing education (586), information booklets developed by nurses (585), a family information leaflet (584), and informational videos with accompanying web-based content (588).

These studies provided limited data for review. ICU education did not appear to impact patients’ anxiety and depression (585, 587, 589), but did improve families’ satisfaction with care (584). The panel judged that education would likely have variable acceptability, as a qualitative study showed that patients who survived sepsis had diverse viewpoints ranging from appreciating the education about sepsis, to not being able to recall the education session, to even disliking it as a reminder of the severity of their condition (588). Based on these data and feedback from the public panel, we suggest that multiple opportunities for education be offered prior to hospital discharge and in the follow-up setting, taking into account patients’ and/or families’ readiness to process information. Sepsis education is regarded as a low cost intervention and feasible, even in low-resource settings, as a number of online and published sepsis education resources exist (590). Future studies are needed to better understand the effects, the cost-effectiveness, and the optimal approach for educating patients and families after sepsis.

## Shared decision making

|  |
| --- |
| Recommendation |
| 1. For adults with sepsis or septic shock and their families, we recommend the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible.   *Best Practice Statement.* |

**Rationale**

Shared decision making (SDM) is a process in which health professionals, patients and their caregivers collaborate in making decisions about a patient’s care options (591). This patient-centered approach may be less routinely used in post-ICU and hospital discharge planning than in other aspects of acute patient care. No studies were identified that compared SDM with other types of ICU or hospital discharge planning. Despite the lack of evidence, SDM in discharge planning as in other care decisions is more likely to result in decisions consistent with the values and preferences of the patient and family. Patient and family involvement in discharge planning may also increase family satisfaction. A small study of ICU relatives found that anxiety and depression rates were lower in those who preferred an active role or shared responsibility in decision-making compared to those who preferred a passive role (592). A family care conference with nursing staff at the time of discharge from the ICU resulted in lower anxiety scores for family members compared to a control group although it is not clear that families participated in SDM (593). Family caregivers of critically ill patients discharged home felt overwhelmed and unprepared and had difficulty managing expectations (594). Communication through SDM at the time of ICU or hospital discharge may improve support for family caregivers as communication was found to be important to decision-making for family surrogates of chronic critically ill patients (595). Studies of tools employed to promote SDM in patients with other serious illnesses show improved patient knowledge and awareness of treatment options (596). Due to the potential benefits of SDM and the current emphasis on patient-centered care, the opportunity for patients and/or family to participate in SDM for ICU and hospital discharge planning is recommended as a best practice statement.

## Discharge planning

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis and septic shock and their families, we suggest using a critical care transition program, compared to usual care, upon transfer to the floor.   *Weak recommendation, very low-quality evidence.* |
| 1. For adults with sepsis and septic shock, we recommend reconciling medications at both ICU and hospital discharge.   *Best Practice Statement.* |
| 1. For adult survivors of sepsis and septic shock and their families, we recommend including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary.   *Best Practice Statement.* |

**Rationale**

Transfer from ICU to general floor and discharge from the hospital are both vulnerable periods for patients, with high frequency of medication errors and information loss (597-603). Sepsis patients, with longer than average hospitalizations and higher comorbidity burden, may be at particular risk for poor outcomes with transitions. Several studies, mostly before-and-after design, have examined the impact of critical care transition programs on reducing ICU readmission or death among patients transferred from ICU to the ward (598, 602, 604-612). These programs have used varied models, but generally involve ICU clinicians (e.g., nurse, respiratory therapist, and/or physician) following patients daily on the wards after transferring out of the ICU for a few days or until clinically stable. Meta-analysis of these studies suggests that critical care transition programs reduce risk of in-hospital mortality and potentially reduce risk of ICU readmission. Effects on ICU workload and workflow have not been systematically examined. Public panel members were supportive of such programs, as they may provide reassurance and a sense of protection to patients after they leave the ICU.

Medication reconciliation is broadly recognized to be important during patient transitions. Hospitalization and ICU admission are high-risk periods for unintentional medication error—both continuations of medications for temporary indications and unintentional discontinuations of chronic medications (597, 600, 601, 603). Medication reconciliation has been associated with fewer medication errors (599, 613) and may help reduce hospital readmission (614, 615). Given the frequency of medication changes during an ICU stay, we recommend reconciling medications at both ICU and hospital discharge. Medication reconciliation surrounding sepsis hospitalization involves getting the correct list of medications and adjusting medication dosing regularly in response to dynamic physiologic changes during and after critical illness (581).

Key information from hospitalization is often missing on hospital discharge documentation (616-619). Information on post-intensive care syndrome (PICS) may be provided to only one in three ICU survivors (551, 619), mechanical ventilation, dialysis), and common impairments after sepsis. Public panel members stressed the importance of providing information in both verbal and written form and assessing that the information was understood. There are a growing number of online resources and informational brochures regarding “post intensive care” / “post-sepsis syndrome" (581), but more research is needed to determine the optimal approaches to providing anticipatory guidance to patients and families after critical illness (583, 620).

|  |
| --- |
| Recommendations |
| 1. For adults with sepsis or septic shock who developed new impairments, we recommend hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae.   *Best Practice Statement.* |
| 1. There is insufficient evidence to make a recommendation on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up. |

**Rationale**

Many sepsis survivors experience short and/or long-term sequela such as cognitive and/or physical disability, with ongoing recovery persisting for months to years (621). Public panelists rated cognitive and physical recovery, psychologic symptoms in survivors and their families, QoL and readmission to the hospital and/or ICU as critically important outcomes. These outcomes were consistent with a 2019 qualitative analysis of health related QoL domains identified by sepsis survivors (622). Follow-up with a provider after hospital discharge is one-step in the recovery process.

Sepsis survivors are at risk for hospital readmission, which has been associated with increased mortality or discharge to hospice (623, 624). Hospital readmission within 90 days of discharge occurs in approximately 40% of sepsis survivors and is associated with high costs (625). Additionally, sepsis survivors are at increased risk for recurrent infection, AKI and new cardiovascular events compared to patients hospitalized for other diagnoses (581). Observational studies in patients with congestive heart failure have associated early (within 7-14 days) post-discharge follow-up with reduced hospital readmissions (626). Among older adults, early post discharge follow-up (within 7 days) with a primary care physician was associated with lower risk of 30-day readmission (627, 628).

Three studies, one RCT (629) and two observational studies (630, 631) evaluated early post-hospital follow-up in patients with critical illness. None of the three studies specifically evaluated a sepsis population or reported the proportion of sepsis patients. The interventions and QoL measures varied among the three studies each with severe limitations. In an analysis of older adults with severe sepsis, one study found that the combination of early home health care and a visit with a medical provider was associated with a reduced readmission risk (632). There were insufficient studies to allow meta-analysis and the limited evidence is of very low quality.

Despite these limitations, the panel recommends follow-up with a provider after hospital discharge to manage new impairments associated with sepsis. Due to the low quality and lack of evidence specific to sepsis, we are unable to make a recommendation for early (7-14 days) provider follow-up versus routine follow-up upon hospital discharge. Timely, coordinated resources and provider follow-up may lead to improved QoL for sepsis survivors, however further research on the impact of post-discharge follow-up is needed.

## Cognitive therapy

|  |
| --- |
| Recommendation |
| 1. There is insufficient evidence to make a recommendation on early cognitive therapy for adult survivors of sepsis or septic shock. |

**Rationale**

Sepsis is associated with newly acquired cognitive impairment and functional disability amongst survivors (621). Long-term impairments in memory, attention, verbal fluency, decision-making and executive functioning may be linked to a variety of mechanisms such as metabolic derangements, cerebral ischemia, overwhelming inflammation, disrupted blood-brain barrier, oxidative stress, and severe microglial activation, particularly within the limbic system (633). A feasibility, pilot, randomized trial in general medical/surgical ICU survivors comparing usual care to an intervention of combined in-home cognitive, physical, and functional rehabilitation following discharge showed improved executive functioning at three months (634). Some small single center studies tested specific early cognitive therapies to enhance cognitive and overall functional recovery after critical illness (635, 636).

A proof-of-concept single-center pilot study aimed to evaluate the efficacy and safety of the use of a multi-faceted early intervention (cognitive therapy within ICU) in patients with respiratory failure and/or shock (635). ICU patients were randomized to receive either combined cognitive and physical therapy or physical therapy alone. The results demonstrated that the intervention was feasible and safe, but the study was underpowered and therefore inconclusive regarding its clinical effects on cognitive function and health-related QoL outcomes at 3-month follow-up. In addition, a prospective cohort study testing a series of cognitive training sessions starting in the ICU and continued for up to two months, found overall minimal clinical relevance as Minimum Clinically Important Difference (MID) of Montreal Cognitive Assessment (MOCA) was small, with some meaningful results in younger patients, but not in the middle-aged or older population (636, 637).

In view of these findings, the panel judged there to be insufficient evidence to make a recommendation. In centers where cognitive therapy is used, it could reasonably be continued as it is likely acceptable and feasible, but there is insufficient evidence to change practice in centers without such therapy. Further larger studies in patients with sepsis are required to determine the impact of early cognitive therapy, as well as costs and type of intervention.

## Post discharge follow up

|  |
| --- |
| Recommendations |
| 1. For adult survivors of sepsis or septic shock, we recommend assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.   Best Practice Statement. |
| 1. For adult survivors of sepsis or septic shock, we suggest referral to a post-critical illness follow-up program if available.   *Weak recommendation, very low-quality evidence.* |
| 1. For adult survivors of sepsis or septic shock receiving mechanical ventilation for >48hours or an ICU stay of >72 hours, we suggest referral to a post-hospital rehabilitation program.   *Weak recommendation, very low-quality evidence.* |

**Rationale**

Given the prevalence of new or worsening physical, cognitive, and emotional problems experienced by sepsis survivors (581, 621), we recommend assessment and follow-up for these problems after hospital discharge. There are insufficient data to suggest any specific tool to assess for these problems, and the optimal approach will vary by patient and setting. At a minimum, physicians should ask patients and families about new problems in these domains.

Post-critical illness programs have been developed as a means of screening for and addressing the multi-faceted issues faced by ICU survivors. These programs vary in their structure, and are not consistently available worldwide (638). Few randomized studies have assessed post-critical illness clinics (589, 629, 639, 640), and—consistent with a recent Cochrane review (641)—our meta-analysis found no differences from usual care in terms of mortality, QoL, physical function, or cognition, with possible small improvements in psychological symptoms (anxiety, depression, PTSD). More studies of post-sepsis follow-up programs are in process (642, 643). We suggest offering referral to post-critical illness clinics where available. While efficacy data are equivocal, these programs are consistently well-liked by patients and offer an environment to learn about challenges sepsis survivors face, as well as to pilot and test interventions for enhancing recovery (638, 644). Lessons learned in post-critical care clinics could be adapted to other, more-scalable interventions such as telehealth.

Several randomized studies have assessed physical rehabilitation programs for survivors of critical illness (582, 607, 645-652). These studies focused on critically ill patients, generally defined by days in ICU or days with mechanical ventilation and begin on the floor or post-hospital setting. Meta-analysis suggests possible small improvements in QoL and depressive symptoms, but no difference in mortality, physical function, or anxiety. Nonetheless, based on their strong rationale, and benefit in related populations (581) (e.g. older patients with cognitive impairment, patients following stroke or traumatic brain injury), we suggest referral to rehabilitation programs in survivors of sepsis. This suggestion is consistent with the guidance of several expert panels (647, 653, 654). Future research is needed to determine an optimal approach to functional rehabilitation (timing, dosing, intensity, duration) and patient selection (644).

# BIBLIOGRAPHY

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.

2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193(3):259-72.

3. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020;46(8):1552-62.

4. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA. 2017;318(13):1241-9.

5. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762-74.

6. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Critical Care Medicine. 2003;31(4):1250-6.

7. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165-228.

8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.

9. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Critical Care Medicine. 2004;32(3):858-73.

10. Dellinger RP, Levy MM, Carlet JM. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 (vol 36, pg 296, 2008). Critical Care Medicine. 2008;36(4):1394-6.

11. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine. 2008;36(1):296-327.

12. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552.

13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.

14. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10-67.

15. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med. 2020;21(2):e52-e106.

16. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64(4):395-400.

17. Akl EA, Johnston BC, Alonso-Coello P, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. PLoS One. 2013;8(2):e57132.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.

19. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

20. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

21. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25.

22. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

23. Schunemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10.

24. Guyatt GH, Schunemann HJ, Djulbegovic B, et al. Guideline panels should not GRADE good practice statements. J Clin Epidemiol. 2015;68(5):597-600.

25. Dellinger RP. The Future of Sepsis Performance Improvement. Critical Care Medicine. 2015;43(9).

26. Schorr C, Odden A, Evans L, et al. Implementation of a multicenter performance improvement program for early detection and treatment of severe sepsis in general medical–surgical wards. Journal of Hospital Medicine. 2016;11(S1):S32-S9.

27. Damiani E, Donati A, Serafini G, et al. Effect of Performance Improvement Programs on Compliance with Sepsis Bundles and Mortality: A Systematic Review and Meta-Analysis of Observational Studies. PLOS ONE. 2015;10(5):e0125827.

28. Alberto L, Marshall AP, Walker R, et al. Screening for sepsis in general hospitalized patients: a systematic review. The Journal of hospital infection. 2017;96(4):305-15.

29. Bhattacharjee P, Edelson DP, Churpek MM. Identifying Patients With Sepsis on the Hospital Wards. CHEST. 2017;151(4):898-907.

30. Makam AN, Nguyen OK, Auerbach AD. Diagnostic accuracy and effectiveness of automated electronic sepsis alert systems: A systematic review. Journal of hospital medicine. 2015;10(6):396-402.

31. Warttig S, Alderson P, Evans DJ, et al. Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients. The Cochrane database of systematic reviews. 2018;6(6):CD012404-CD.

32. Islam MM, Nasrin T, Walther BA, et al. Prediction of sepsis patients using machine learning approach: A meta-analysis. Computer Methods and Programs in Biomedicine. 2019;170:1-9.

33. Downing NL, Rolnick J, Poole SF, et al. Electronic health record-based clinical decision support alert for severe sepsis: a randomised evaluation. BMJ Qual Saf. 2019;28(9):762-8.

34. Hooper MH, Weavind L, Wheeler AP, et al. Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit\*. Critical care medicine. 2012;40(7):2096-101.

35. Shimabukuro DW, Barton CW, Feldman MD, et al. Effect of a machine learning-based severe sepsis prediction algorithm on patient survival and hospital length of stay: a randomised clinical trial. BMJ Open Respiratory Research. 2017;4(1):e000234.

36. Rao TSS, Radhakrishnan R, Andrade C. Standard operating procedures for clinical practice. Indian J Psychiatry. 2011;53(1):1-3.

37. Osborn TM. Severe Sepsis and Septic Shock Trials (ProCESS, ARISE, ProMISe): What is Optimal Resuscitation? Crit Care Clin. 2017;33(2):323-44.

38. Kahn JM, Davis BS, Yabes JG, et al. Association Between State-Mandated Protocolized Sepsis Care and In-hospital Mortality Among Adults With Sepsis. JAMA. 2019;322(3):240-50.

39. Morton B, Stolbrink M, Kagima W, et al. The Early Recognition and Management of Sepsis in Sub-Saharan African Adults: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2018;15(9):2017.

40. Fernando SM, Tran A, Taljaard M, et al. Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection: A Systematic Review and Meta-analysis. Ann Intern Med. 2018;168(4):266-75.

41. Herwanto V, Shetty A, Nalos M, et al. Accuracy of Quick Sequential Organ Failure Assessment Score to Predict Sepsis Mortality in 121 Studies Including 1,716,017 Individuals: A Systematic Review and Meta-Analysis. Crit Care Explor. 2019;1(9):e0043.

42. Serafim R, Gomes JA, Salluh J, et al. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality: A Systematic Review and Meta-Analysis. Chest. 2018;153(3):646-55.

43. Cinel I, Kasapoglu US, Gul F, et al. The initial resuscitation of septic shock. J Crit Care. 2020;57:108-17.

44. Liu VX, Lu Y, Carey KA, et al. Comparison of Early Warning Scoring Systems for Hospitalized Patients With and Without Infection at Risk for In-Hospital Mortality and Transfer to the Intensive Care Unit. JAMA Netw Open. 2020;3(5):e205191.

45. Borthwick HA, Brunt LK, Mitchem KL, et al. Does lactate measurement performed on admission predict clinical outcome on the intensive care unit? A concise systematic review. Ann Clin Biochem. 2012;49(Pt 4):391-4.

46. Liu G, An Y, Yi X, et al. Early lactate levels for prediction of mortality in patients with sepsis or septic shock: a meta-analysis. . Int J Exp Med. 2017;10:37-47.

47. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 Update. Crit Care Med. 2018;46(6):997-1000.

48. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018;44(6):925-8.

49. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775-87.

50. Contenti J, Corraze H, Lemoel F, et al. Effectiveness of arterial, venous, and capillary blood lactate as a sepsis triage tool in ED patients. Am J Emerg Med. 2015;33(2):167-72.

51. Karon BS, Tolan NV, Wockenfus AM, et al. Evaluation of lactate, white blood cell count, neutrophil count, procalcitonin and immature granulocyte count as biomarkers for sepsis in emergency department patients. Clin Biochem. 2017;50(16-17):956-8.

52. Ljungstrom L, Pernestig AK, Jacobsson G, et al. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One. 2017;12(7):e0181704.

53. Morris E, McCartney D, Lasserson D, et al. Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. Br J Gen Pract. 2017;67(665):e859-e70.

54. Abdu M, Wilson A, Mhango C, et al. Resource availability for the management of maternal sepsis in Malawi, other low-income countries, and lower-middle-income countries. Int J Gynaecol Obstet. 2018;140(2):175-83.

55. Baelani I, Jochberger S, Laimer T, et al. Availability of critical care resources to treat patients with severe sepsis or septic shock in Africa: a self-reported, continent-wide survey of anaesthesia providers. Crit Care. 2011;15(1):R10.

56. Baelani I, Jochberger S, Laimer T, et al. Identifying resource needs for sepsis care and guideline implementation in the Democratic Republic of the Congo: a cluster survey of 66 hospitals in four eastern provinces. Middle East J Anaesthesiol. 2012;21(4):559-75.

57. Bataar O, Lundeg G, Tsenddorj G, et al. Nationwide survey on resource availability for implementing current sepsis guidelines in Mongolia. Bull World Health Organ. 2010;88(11):839-46.

58. Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654-64.

59. Machado FR, Cavalcanti AB, Bozza FA, et al. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. Lancet Infect Dis. 2017;17(11):1180-9.

60. Shrestha GS, Kwizera A, Lundeg G, et al. International Surviving Sepsis Campaign guidelines 2016: the perspective from low-income and middle-income countries. Lancet Infect Dis. 2017;17(9):893-5.

61. Taniguchi LU, Azevedo LCP, Bozza FA, et al. Availability of resources to treat sepsis in Brazil: a random sample of Brazilian institutions. Rev Bras Ter Intensiva. 2019;31(2):193-201.

62. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med. 2010;36(2):222-31.

63. Kuttab HI, Lykins JD, Hughes MD, et al. Evaluation and Predictors of Fluid Resuscitation in Patients With Severe Sepsis and Septic Shock. Crit Care Med. 2019;47(11):1582-90.

64. Investigators P, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683-93.

65. Peake SL, Delaney A, Bellomo R, et al. Goal-directed resuscitation in septic shock. N Engl J Med. 2015;372(2):190-1.

66. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-11.

67. Rowan KM, Angus DC, Bailey M, et al. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med. 2017;376(23):2223-34.

68. Ehrman RR, Gallien JZ, Smith RK, et al. Resuscitation Guided by Volume Responsiveness Does Not Reduce Mortality in Sepsis: A Meta-Analysis. Crit Care Explor. 2019;1(5):e0015.

69. Andrews B, Semler MW, Muchemwa L, et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial. JAMA. 2017;318(13):1233-40.

70. Aya HD, Rhodes A, Chis Ster I, et al. Hemodynamic Effect of Different Doses of Fluids for a Fluid Challenge: A Quasi-Randomized Controlled Study. Crit Care Med. 2017;45(2):e161-e8.

71. Cherpanath TG, Hirsch A, Geerts BF, et al. Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials. Crit Care Med. 2016;44(5):981-91.

72. Misango D, Pattnaik R, Baker T, et al. Haemodynamic assessment and support in sepsis and septic shock in resource-limited settings. Trans R Soc Trop Med Hyg. 2017;111(11):483-9.

73. Levy B. Lactate and shock state: the metabolic view. Curr Opin Crit Care. 2006;12(4):315-21.

74. Gu WJ, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. Intensive Care Med. 2015;41(10):1862-3.

75. Simpson SQ, Gaines M, Hussein Y, et al. Early goal-directed therapy for severe sepsis and septic shock: A living systematic review. J Crit Care. 2016;36:43-8.

76. Cecconi M, Hernandez G, Dunser M, et al. Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force. Intensive Care Med. 2019;45(1):21-32.

77. Lara B, Enberg L, Ortega M, et al. Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. PLoS One. 2017;12(11):e0188548.

78. Shrestha GS, Dunser M, Mer M. The forgotten value of the clinical examination to individualize and guide fluid resuscitation in patients with sepsis. Crit Care. 2017;21(1):306.

79. LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med. 2000;28(8):2729-32.

80. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583-93.

81. Hylands M, Moller MH, Asfar P, et al. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth. 2017;64(7):703-15.

82. Lamontagne F, Meade MO, Hebert PC, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive Care Med. 2016;42(4):542-50.

83. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. JAMA. 2020;323(10):938-49.

84. Mohr NM, Wessman BT, Bassin B, et al. Boarding of Critically Ill Patients in the Emergency Department. Crit Care Med. 2020;48(8):1180-7.

85. Cardoso LT, Grion CM, Matsuo T, et al. Impact of delayed admission to intensive care units on mortality of critically ill patients: a cohort study. Crit Care. 2011;15(1):R28.

86. Groenland CNL, Termorshuizen F, Rietdijk WJR, et al. Emergency Department to ICU Time Is Associated With Hospital Mortality: A Registry Analysis of 14,788 Patients From Six University Hospitals in The Netherlands. Crit Care Med. 2019;47(11):1564-71.

87. Chalfin DB, Trzeciak S, Likourezos A, et al. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med. 2007;35(6):1477-83.

88. Harris S, Singer M, Sanderson C, et al. Impact on mortality of prompt admission to critical care for deteriorating ward patients: an instrumental variable analysis using critical care bed strain. Intensive Care Med. 2018;44(5):606-15.

89. Montgomery A, Panagopoulou E, Kehoe I, et al. Connecting organisational culture and quality of care in the hospital: is job burnout the missing link? J Health Organ Manag. 2011;25(1):108-23.

90. Klein Klouwenberg PM, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015;19:319.

91. Levin PD, Idrees S, Sprung CL, et al. Antimicrobial use in the ICU: indications and accuracy--an observational trial. J Hosp Med. 2012;7(9):672-8.

92. Minderhoud TC, Spruyt C, Huisman S, et al. Microbiological outcomes and antibiotic overuse in Emergency Department patients with suspected sepsis. Neth J Med. 2017;75(5):196-203.

93. Heffner AC, Horton JM, Marchick MR, et al. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis. 2010;50(6):814-20.

94. Tidswell R, Parker T, Brealey D, et al. Sepsis - the broken code how accurately is sepsis being diagnosed? J Infect. 2020.

95. Deuster S, Roten I, Muehlebach S. Implementation of treatment guidelines to support judicious use of antibiotic therapy. J Clin Pharm Ther. 2010;35(1):71-8.

96. Ferrer R, Artigas A, Suarez D, et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med. 2009;180(9):861-6.

97. Kalil AC, Johnson DW, Lisco SJ, et al. Early Goal-Directed Therapy for Sepsis: A Novel Solution for Discordant Survival Outcomes in Clinical Trials. Crit Care Med. 2017;45(4):607-14.

98. Seymour CW, Gesten F, Prescott HC, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376(23):2235-44.

99. Klompas M, Calandra T, Singer M. Antibiotics for Sepsis-Finding the Equilibrium. JAMA. 2018;320(14):1433-4.

100. Prescott HC, Iwashyna TJ. Improving Sepsis Treatment by Embracing Diagnostic Uncertainty. Ann Am Thorac Soc. 2019;16(4):426-9.

101. Baggs J, Jernigan JA, Halpin AL, et al. Risk of Subsequent Sepsis Within 90 Days After a Hospital Stay by Type of Antibiotic Exposure. Clin Infect Dis. 2018;66(7):1004-12.

102. Branch-Elliman W, O'Brien W, Strymish J, et al. Association of Duration and Type of Surgical Prophylaxis With Antimicrobial-Associated Adverse Events. JAMA Surg. 2019;154(7):590-8.

103. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet Infect Dis. 2012;12(10):774-80.

104. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al. Short-Course Adjunctive Gentamicin as Empirical Therapy in Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study. Clin Infect Dis. 2017;64(12):1731-6.

105. Tamma PD, Avdic E, Li DX, et al. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. JAMA Intern Med. 2017;177(9):1308-15.

106. Teshome BF, Vouri SM, Hampton N, et al. Duration of Exposure to Antipseudomonal beta-Lactam Antibiotics in the Critically Ill and Development of New Resistance. Pharmacotherapy. 2019;39(3):261-70.

107. Contou D, Roux D, Jochmans S, et al. Septic shock with no diagnosis at 24 hours: a pragmatic multicenter prospective cohort study. Crit Care. 2016;20(1):360.

108. Rhee C, Kadri SS, Danner RL, et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. Crit Care. 2016;20:89.

109. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.

110. Liu VX, Fielding-Singh V, Greene JD, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. Am J Respir Crit Care Med. 2017;196(7):856-63.

111. Peltan ID, Brown SM, Bledsoe JR, et al. ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis. Chest. 2019;155(5):938-46.

112. Abe T, Kushimoto S, Tokuda Y, et al. Implementation of earlier antibiotic administration in patients with severe sepsis and septic shock in Japan: a descriptive analysis of a prospective observational study. Crit Care. 2019;23(1):360.

113. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010;38(4):1045-53.

114. Ko BS, Choi SH, Kang GH, et al. Time to Antibiotics and the Outcome of Patients with Septic Shock: A Propensity Score Analysis. Am J Med. 2020;133(4):485-91 e4.

115. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med. 2011;39(9):2066-71.

116. Rothrock SG, Cassidy DD, Barneck M, et al. Outcome of Immediate Versus Early Antibiotics in Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. Ann Emerg Med. 2020.

117. Ryoo SM, Kim WY, Sohn CH, et al. Prognostic value of timing of antibiotic administration in patients with septic shock treated with early quantitative resuscitation. Am J Med Sci. 2015;349(4):328-33.

118. Weinberger J, Rhee C, Klompas M. A Critical Analysis of the Literature on Time-to-Antibiotics in Suspected Sepsis. J Infect Dis. 2020;222(Supplement\_2):S110-S8.

119. Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med. 2018;6(1):40-50.

120. Bloos F, Ruddel H, Thomas-Ruddel D, et al. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med. 2017;43(11):1602-12.

121. Chalya PL, Mabula JB, Koy M, et al. Typhoid intestinal perforations at a University teaching hospital in Northwestern Tanzania: A surgical experience of 104 cases in a resource-limited setting. World J Emerg Surg. 2012;7:4.

122. Phua J, Koh Y, Du B, et al. Management of severe sepsis in patients admitted to Asian intensive care units: prospective cohort study. BMJ. 2011;342:d3245.

123. Thwaites CL, Lundeg G, Dondorp AM, et al. Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings. Intensive Care Med. 2016;42(12):2040-2.

124. Urayeneza O, Mujyarugamba P, Rukemba Z, et al. Increasing Evidence-Based Interventions in Patients with Acute Infections in a Resource-Limited Setting: A Before-and-After Feasibility Trial in Gitwe, Rwanda. Crit Care Med. 2018;46(8):1357-66.

125. Urayeneza O, Mujyarugamba P, Rukemba Z, et al. Increasing evidence-based interventions in patients with acute infections in a resource-limited setting: a before-and-after feasibility trial in Gitwe, Rwanda. Intensive Care Med. 2018;44(9):1436-46.

126. Yokota PK, Marra AR, Martino MD, et al. Impact of appropriate antimicrobial therapy for patients with severe sepsis and septic shock--a quality improvement study. PLoS One. 2014;9(11):e104475.

127. Peng F, Chang W, Xie JF, et al. Ineffectiveness of procalcitonin-guided antibiotic therapy in severely critically ill patients: A meta-analysis. Int J Infect Dis. 2019;85:158-66.

128. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(5):426-35.

129. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med. 2011;39(9):2048-58.

130. Layios N, Lambermont B, Canivet JL, et al. Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. Crit Care Med. 2012;40(8):2304-9.

131. Najafi A, Khodadadian A, Sanatkar M, et al. The Comparison of Procalcitonin Guidance Administer Antibiotics with Empiric Antibiotic Therapy in Critically Ill Patients Admitted in Intensive Care Unit. Acta Med Iran. 2015;53(9):562-7.

132. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.

133. Vincent JL, Sakr Y, Singer M, et al. Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017. JAMA. 2020.

134. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012-2017. N Engl J Med. 2020;382(14):1309-19.

135. Jones M, Jernigan JA, Evans ME, et al. Vital Signs: Trends in Staphylococcus aureus Infections in Veterans Affairs Medical Centers - United States, 2005-2017. MMWR Morb Mortal Wkly Rep. 2019;68(9):220-4.

136. Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. Lancet Infect Dis. 2016;16(12):1364-76.

137. Rhee C, Kadri SS, Dekker JP, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open. 2020;3(4):e202899.

138. Callejo-Torre F, Eiros Bouza JM, Olaechea Astigarraga P, et al. Risk factors for methicillin-resistant Staphylococcus aureus colonisation or infection in intensive care units and their reliability for predicting MRSA on ICU admission. Infez Med. 2016;24(3):201-9.

139. Epstein L, Mu Y, Belflower R, et al. Risk Factors for Invasive Methicillin-Resistant Staphylococcus aureus Infection After Recent Discharge From an Acute-Care Hospitalization, 2011-2013. Clin Infect Dis. 2016;62(1):45-52.

140. Shorr AF, Myers DE, Huang DB, et al. A risk score for identifying methicillin-resistant Staphylococcus aureus in patients presenting to the hospital with pneumonia. BMC Infect Dis. 2013;13:268.

141. Torre-Cisneros J, Natera C, Mesa F, et al. Clinical predictors of methicillin-resistant Staphylococcus aureus in nosocomial and healthcare-associated pneumonia: a multicenter, matched case-control study. Eur J Clin Microbiol Infect Dis. 2018;37(1):51-6.

142. Wooten DA, Winston LG. Risk factors for methicillin-resistant Staphylococcus aureus in patients with community-onset and hospital-onset pneumonia. Respir Med. 2013;107(8):1266-70.

143. Gasch O, Camoez M, Dominguez MA, et al. Predictive factors for early mortality among patients with methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2013;68(6):1423-30.

144. Gasch O, Camoez M, Dominguez MA, et al. Predictive factors for mortality in patients with methicillin-resistant Staphylococcus aureus bloodstream infection: impact on outcome of host, microorganism and therapy. Clin Microbiol Infect. 2013;19(11):1049-57.

145. Lodise TP, McKinnon PS, Swiderski L, et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis. 2003;36(11):1418-23.

146. Paul M, Kariv G, Goldberg E, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2010;65(12):2658-65.

147. Schramm GE, Johnson JA, Doherty JA, et al. Methicillin-resistant Staphylococcus aureus sterile-site infection: The importance of appropriate initial antimicrobial treatment. Crit Care Med. 2006;34(8):2069-74.

148. Fang CT, Shau WY, Hsueh PR, et al. Early empirical glycopeptide therapy for patients with methicillin-resistant Staphylococcus aureus bacteraemia: impact on the outcome. J Antimicrob Chemother. 2006;57(3):511-9.

149. Gomez J, Garcia-Vazquez E, Banos R, et al. Predictors of mortality in patients with methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia: the role of empiric antibiotic therapy. Eur J Clin Microbiol Infect Dis. 2007;26(4):239-45.

150. Griffin AT, Peyrani P, Wiemken TL, et al. Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia. Infection. 2013;41(2):517-23.

151. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis. 2011;11(3):181-9.

152. Khatib R, Saeed S, Sharma M, et al. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2006;25(3):181-5.

153. Kim SH, Park WB, Lee KD, et al. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2004;54(2):489-97.

154. Yoon YK, Park DW, Sohn JW, et al. Effects of inappropriate empirical antibiotic therapy on mortality in patients with healthcare-associated methicillin-resistant Staphylococcus aureus bacteremia: a propensity-matched analysis. BMC Infect Dis. 2016;16:331.

155. Jones BE, Ying J, Stevens V, et al. Empirical Anti-MRSA vs Standard Antibiotic Therapy and Risk of 30-Day Mortality in Patients Hospitalized for Pneumonia. JAMA Intern Med. 2020.

156. Webb BJ, Sorensen J, Jephson A, et al. Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. Eur Respir J. 2019;54(1).

157. Baby N, Faust AC, Smith T, et al. Nasal Methicillin-Resistant Staphylococcus aureus (MRSA) PCR Testing Reduces the Duration of MRSA-Targeted Therapy in Patients with Suspected MRSA Pneumonia. Antimicrob Agents Chemother. 2017;61(4).

158. Cowley MC, Ritchie DJ, Hampton N, et al. Outcomes Associated With De-escalating Therapy for Methicillin-Resistant Staphylococcus aureus in Culture-Negative Nosocomial Pneumonia. Chest. 2019;155(1):53-9.

159. Paonessa JR, Shah RD, Pickens CI, et al. Rapid Detection of Methicillin-Resistant Staphylococcus aureus in BAL: A Pilot Randomized Controlled Trial. Chest. 2019;155(5):999-1007.

160. Sjovall F, Perner A, Hylander Moller M. Empirical mono- versus combination antibiotic therapy in adult intensive care patients with severe sepsis - A systematic review with meta-analysis and trial sequential analysis. J Infect. 2017;74(4):331-44.

161. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. JAMA. 2012;307(22):2390-9.

162. Alevizakos M, Karanika S, Detsis M, et al. Colonisation with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk for infection among patients with solid or haematological malignancy: a systematic review and meta-analysis. Int J Antimicrob Agents. 2016;48(6):647-54.

163. Rottier WC, Bamberg YR, Dorigo-Zetsma JW, et al. Predictive value of prior colonization and antibiotic use for third-generation cephalosporin-resistant enterobacteriaceae bacteremia in patients with sepsis. Clin Infect Dis. 2015;60(11):1622-30.

164. Rottier WC, van Werkhoven CH, Bamberg YRP, et al. Development of diagnostic prediction tools for bacteraemia caused by third-generation cephalosporin-resistant enterobacteria in suspected bacterial infections: a nested case-control study. Clin Microbiol Infect. 2018;24(12):1315-21.

165. Arulkumaran N, Routledge M, Schlebusch S, et al. Antimicrobial-associated harm in critical care: a narrative review. Intensive Care Med. 2020;46(2):225-35.

166. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med. 2014;40(6):839-45.

167. Kollef M, Micek S, Hampton N, et al. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis. 2012;54(12):1739-46.

168. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198-208.

169. Mean M, Marchetti O, Calandra T. Bench-to-bedside review: Candida infections in the intensive care unit. Crit Care. 2008;12(1):204.

170. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.

171. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. 2006;43(1):25-31.

172. Marriott DJ, Playford EG, Chen S, et al. Determinants of mortality in non-neutropenic ICU patients with candidaemia. Crit Care. 2009;13(4):R115.

173. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother. 2005;49(9):3640-5.

174. Timsit JF, Azoulay E, Schwebel C, et al. Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure: The EMPIRICUS Randomized Clinical Trial. JAMA. 2016;316(15):1555-64.

175. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56-93.

176. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36(14):1443-53.

177. Clancy CJ, Nguyen MH. Diagnosing Invasive Candidiasis. J Clin Microbiol. 2018;56(5).

178. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015;373(15):1445-56.

179. Sandven P, Qvist H, Skovlund E, et al. Significance of Candida recovered from intraoperative specimens in patients with intra-abdominal perforations. Crit Care Med. 2002;30(3):541-7.

180. Hachem R, Hanna H, Kontoyiannis D, et al. The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer. 2008;112(11):2493-9.

181. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48(12):1695-703.

182. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012;54(8):1110-22.

183. Kett DH, Azoulay E, Echeverria PM, et al. Candida bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med. 2011;39(4):665-70.

184. Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PLoS One. 2015;10(3):e0120452.

185. Zhang AY, Shrum S, Williams S, et al. The Changing Epidemiology of Candidemia in the United States: Injection Drug Use as an Increasingly Common Risk Factor-Active Surveillance in Selected Sites, United States, 2014-2017. Clin Infect Dis. 2020;71(7):1732-7.

186. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis. 2001;33(2):177-86.

187. Fan D, Coughlin LA, Neubauer MM, et al. Activation of HIF-1alpha and LL-37 by commensal bacteria inhibits Candida albicans colonization. Nat Med. 2015;21(7):808-14.

188. Chow JK, Golan Y, Ruthazer R, et al. Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit Care Med. 2008;36(7):1993-8.

189. Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. Crit Care Med. 2006;34(3):857-63.

190. Vergidis P, Clancy CJ, Shields RK, et al. Intra-Abdominal Candidiasis: The Importance of Early Source Control and Antifungal Treatment. PLoS One. 2016;11(4):e0153247.

191. Ballard N, Robley L, Barrett D, et al. Patients' recollections of therapeutic paralysis in the intensive care unit. American journal of critical care : an official publication, American Association of Critical-Care Nurses. 2006;15(1):86-94; quiz 5.

192. Horvath EE, Murray CK, Vaughan GM, et al. Fungal wound infection (not colonization) is independently associated with mortality in burn patients. Ann Surg. 2007;245(6):978-85.

193. Murray CK, Loo FL, Hospenthal DR, et al. Incidence of systemic fungal infection and related mortality following severe burns. Burns. 2008;34(8):1108-12.

194. Baughman RP, Rhodes JC, Dohn MN, et al. Detection of cryptococcal antigen in bronchoalveolar lavage fluid: a prospective study of diagnostic utility. Am Rev Respir Dis. 1992;145(5):1226-9.

195. Ford N, Shubber Z, Jarvis JN, et al. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;66(suppl\_2):S152-S9.

196. Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448-54.

197. Clumeck N, Sonnet J, Taelman H, et al. Acquired immunodeficiency syndrome in African patients. N Engl J Med. 1984;310(8):492-7.

198. Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis. 1999;179(2):449-54.

199. Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2016;30(1):179-206.

200. McCarthy KM, Morgan J, Wannemuehler KA, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS. 2006;20(17):2199-206.

201. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7(3):375-81.

202. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101-11.

203. Singh N, Gayowski T, Wagener MM, et al. Clinical spectrum of invasive cryptococcosis in liver transplant recipients receiving tacrolimus. Clin Transplant. 1997;11(1):66-70.

204. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50(8):1091-100.

205. Nath DS, Kandaswamy R, Gruessner R, et al. Fungal infections in transplant recipients receiving alemtuzumab. Transplant Proc. 2005;37(2):934-6.

206. Tsiodras S, Samonis G, Boumpas DT, et al. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008;83(2):181-94.

207. Nsenga L, Kajjimu J, Olum R, et al. Cryptococcosis complicating diabetes mellitus: a scoping review. Ther Adv Infect Dis. 2021;8:20499361211014769.

208. Wald A, Leisenring W, van Burik JA, et al. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis. 1997;175(6):1459-66.

209. Mengoli C, Cruciani M, Barnes RA, et al. Use of PCR for diagnosis of invasive aspergillosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9(2):89-96.

210. White PL, Bretagne S, Klingspor L, et al. Aspergillus PCR: one step closer to standardization. J Clin Microbiol. 2010;48(4):1231-40.

211. White PL, Wingard JR, Bretagne S, et al. Aspergillus Polymerase Chain Reaction: Systematic Review of Evidence for Clinical Use in Comparison With Antigen Testing. Clin Infect Dis. 2015;61(8):1293-303.

212. Meersseman W, Lagrou K, Maertens J, et al. Invasive aspergillosis in the intensive care unit. Clin Infect Dis. 2007;45(2):205-16.

213. Barnes PD, Marr KA. Aspergillosis: spectrum of disease, diagnosis, and treatment. Infect Dis Clin North Am. 2006;20(3):545-61, vi.

214. Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis. 2005;41(1):52-9.

215. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood. 2003;102(3):827-33.

216. Pagano L, Busca A, Candoni A, et al. Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations. Blood Rev. 2017;31(2):17-29.

217. Baddley JW. Clinical risk factors for invasive aspergillosis. Med Mycol. 2011;49 Suppl 1:S7-S12.

218. Ruiz-Camps I, Aguilar-Company J. Risk of infection associated with targeted therapies for solid organ and hematological malignancies. Ther Adv Infect Dis. 2021;8:2049936121989548.

219. Cantan B, Luyt CE, Martin-Loeches I. Influenza Infections and Emergent Viral Infections in Intensive Care Unit. Semin Respir Crit Care Med. 2019;40(4):488-97.

220. Legoff J, Zucman N, Lemiale V, et al. Clinical Significance of Upper Airway Virus Detection in Critically Ill Hematology Patients. Am J Respir Crit Care Med. 2019;199(4):518-28.

221. Muscedere J, Ofner M, Kumar A, et al. The occurrence and impact of bacterial organisms complicating critical care illness associated with 2009 influenza A(H1N1) infection. Chest. 2013;144(1):39-47.

222. van Someren Greve F, Juffermans NP, Bos LDJ, et al. Respiratory Viruses in Invasively Ventilated Critically Ill Patients-A Prospective Multicenter Observational Study. Crit Care Med. 2018;46(1):29-36.

223. Aziz S, Arabi YM, Alhazzani W, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med. 2020.

224. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-93.

225. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014;2(5):395-404.

226. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46(5):854-87.

227. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47(3):303-27.

228. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis. 2019;68(6):895-902.

229. Lin GL, McGinley JP, Drysdale SB, et al. Epidemiology and Immune Pathogenesis of Viral Sepsis. Front Immunol. 2018;9:2147.

230. Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care. 2011;15(5):R206.

231. Mohd Hafiz AA, Staatz CE, Kirkpatrick CM, et al. Continuous infusion vs. bolus dosing: implications for beta-lactam antibiotics. Minerva Anestesiol. 2012;78(1):94-104.

232. Roberts JA, Abdul-Aziz MH, Davis JS, et al. Continuous versus Intermittent beta-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials. Am J Respir Crit Care Med. 2016;194(6):681-91.

233. Vardakas KZ, Voulgaris GL, Maliaros A, et al. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis. 2018;18(1):108-20.

234. De Waele JJ, Lipman J, Carlier M, et al. Subtleties in practical application of prolonged infusion of beta-lactam antibiotics. Int J Antimicrob Agents. 2015;45(5):461-3.

235. Roberts JA, Paratz J, Paratz E, et al. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents. 2007;30(1):11-8.

236. Lipman J, Brett SJ, De Waele JJ, et al. A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent beta-lactam antibiotic infusion in critically ill patients with sepsis: BLING III. Crit Care Resusc. 2019;21(1):63-8.

237. Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498-509.

238. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014;58(8):1072-83.

239. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. Crit Care. 2018;22(1):233.

240. Nelson NR, Morbitzer KA, Jordan JD, et al. The Impact of Capping Creatinine Clearance on Achieving Therapeutic Vancomycin Concentrations in Neurocritically Ill Patients with Traumatic Brain Injury. Neurocrit Care. 2019;30(1):126-31.

241. Gregoire N, Marchand S, Ferrandiere M, et al. Population pharmacokinetics of daptomycin in critically ill patients with various degrees of renal impairment. J Antimicrob Chemother. 2019;74(1):117-25.

242. Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99-110.

243. Choi G, Gomersall CD, Tian Q, et al. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med. 2009;37(7):2268-82.

244. Roberts JA, Joynt G, Lee A, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: Data from the multinational SMARRT Study. Clin Infect Dis. 2020.

245. Bougle A, Dujardin O, Lepere V, et al. PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support. Anaesth Crit Care Pain Med. 2019;38(5):493-7.

246. Cheng V, Abdul-Aziz MH, Roberts JA, et al. Overcoming barriers to optimal drug dosing during ECMO in critically ill adult patients. Expert Opin Drug Metab Toxicol. 2019;15(2):103-12.

247. Guilhaumou R, Benaboud S, Bennis Y, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Societe Francaise de Pharmacologie et Therapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Societe Francaise d'Anesthesie et Reanimation-SFAR). Crit Care. 2019;23(1):104.

248. Turner RB, Kojiro K, Shephard EA, et al. Review and Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of the Vancomycin Area Under the Curve in Critically Ill Patients. Pharmacotherapy. 2018;38(12):1174-83.

249. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66(1):82-98.

250. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents. 2008;31(4):345-51.

251. Rayner CR, Forrest A, Meagher AK, et al. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet. 2003;42(15):1411-23.

252. Rubino CM, Bhavnani SM, Forrest A, et al. Pharmacokinetics-pharmacodynamics of tigecycline in patients with community-acquired pneumonia. Antimicrob Agents Chemother. 2012;56(1):130-6.

253. Wong G, Taccone F, Villois P, et al. beta-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill. J Antimicrob Chemother. 2020;75(2):429-33.

254. Fleuren LM, Roggeveen LF, Guo T, et al. Clinically relevant pharmacokinetic knowledge on antibiotic dosing among intensive care professionals is insufficient: a cross-sectional study. Crit Care. 2019;23(1):185.

255. Ehmann L, Zoller M, Minichmayr IK, et al. Development of a dosing algorithm for meropenem in critically ill patients based on a population pharmacokinetic/pharmacodynamic analysis. Int J Antimicrob Agents. 2019;54(3):309-17.

256. Wong G, Briscoe S, McWhinney B, et al. Therapeutic drug monitoring of beta-lactam antibiotics in the critically ill: direct measurement of unbound drug concentrations to achieve appropriate drug exposures. J Antimicrob Chemother. 2018;73(11):3087-94.

257. Williams P, Beall G, Cotta MO, et al. Antimicrobial dosing in critical care: A pragmatic adult dosing nomogram. Int J Antimicrob Agents. 2020;55(2):105837.

258. Williams P, Cotta MO, Roberts JA. Pharmacokinetics/Pharmacodynamics of beta-Lactams and Therapeutic Drug Monitoring: From Theory to Practical Issues in the Intensive Care Unit. Semin Respir Crit Care Med. 2019;40(4):476-87.

259. Nation RL, Garonzik SM, Thamlikitkul V, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis. 2017;64(5):565-71.

260. Roberts JA, Taccone FS, Udy AA, et al. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother. 2011;55(6):2704-9.

261. Sinnollareddy M, Peake SL, Roberts MS, et al. Using pharmacokinetics and pharmacodynamics to optimise dosing of antifungal agents in critically ill patients: a systematic review. Int J Antimicrob Agents. 2012;39(1):1-10.

262. Jimenez MF, Marshall JC, International Sepsis F. Source control in the management of sepsis. Intensive Care Med. 2001;27 Suppl 1:S49-62.

263. Kim H, Chung SP, Choi SH, et al. Impact of timing to source control in patients with septic shock: A prospective multi-center observational study. J Crit Care. 2019;53:176-82.

264. Martinez ML, Ferrer R, Torrents E, et al. Impact of Source Control in Patients With Severe Sepsis and Septic Shock. Crit Care Med. 2017;45(1):11-9.

265. Azuhata T, Kinoshita K, Kawano D, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18(3):R87.

266. Bloos F, Thomas-Ruddel D, Ruddel H, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care. 2014;18(2):R42.

267. Buck DL, Vester-Andersen M, Moller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg. 2013;100(8):1045-9.

268. Chao WN, Tsai CF, Chang HR, et al. Impact of timing of surgery on outcome of Vibrio vulnificus-related necrotizing fasciitis. Am J Surg. 2013;206(1):32-9.

269. Karvellas CJ, Abraldes JG, Zepeda-Gomez S, et al. The impact of delayed biliary decompression and anti-microbial therapy in 260 patients with cholangitis-associated septic shock. Aliment Pharmacol Ther. 2016;44(7):755-66.

270. Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. J Pediatr Surg. 1996;31(8):1142-6.

271. Wong CH, Chang HC, Pasupathy S, et al. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am. 2003;85(8):1454-60.

272. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133-64.

273. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45.

274. Rijnders BJ, Peetermans WE, Verwaest C, et al. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med. 2004;30(6):1073-80.

275. Garnacho-Montero J, Aldabo-Pallas T, Palomar-Martinez M, et al. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. Intensive Care Med. 2008;34(12):2185-93.

276. Lorente L, Martin MM, Vidal P, et al. Should central venous catheter be systematically removed in patients with suspected catheter related infection? Crit Care. 2014;18(5):564.

277. Tabah A, Bassetti M, Kollef MH, et al. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). Intensive Care Med. 2020;46(2):245-65.

278. Leone M, Bechis C, Baumstarck K, et al. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med. 2014;40(10):1399-408.

279. Tabah A, Cotta MO, Garnacho-Montero J, et al. A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit. Clin Infect Dis. 2016;62(8):1009-17.

280. De Bus L, Depuydt P, Steen J, et al. Antimicrobial de-escalation in the critically ill patient and assessment of clinical cure: the DIANA study. Intensive Care Med. 2020.

281. Fernandez-Lazaro CI, Brown KA, Langford BJ, et al. Late-career Physicians Prescribe Longer Courses of Antibiotics. Clin Infect Dis. 2019;69(9):1467-75.

282. Hanretty AM, Gallagher JC. Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy. 2018;38(6):674-87.

283. Royer S, DeMerle KM, Dickson RP, et al. Shorter Versus Longer Courses of Antibiotics for Infection in Hospitalized Patients: A Systematic Review and Meta-Analysis. J Hosp Med. 2018;13(5):336-42.

284. Spellberg B. The New Antibiotic Mantra-"Shorter Is Better". JAMA Intern Med. 2016;176(9):1254-5.

285. Wald-Dickler N, Spellberg B. Short-course Antibiotic Therapy-Replacing Constantine Units With "Shorter Is Better". Clin Infect Dis. 2019;69(9):1476-9.

286. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003;290(19):2588-98.

287. Choudhury G, Mandal P, Singanayagam A, et al. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia--a propensity-adjusted analysis. Clin Microbiol Infect. 2011;17(12):1852-8.

288. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111.

289. Vaughn VM, Flanders SA, Snyder A, et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med. 2019;171(3):153-63.

290. Eliakim-Raz N, Yahav D, Paul M, et al. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-- 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2013;68(10):2183-91.

291. Runyon BA, McHutchison JG, Antillon MR, et al. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology. 1991;100(6):1737-42.

292. Yahav D, Franceschini E, Koppel F, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. Clin Infect Dis. 2019;69(7):1091-8.

293. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996-2005.

294. Corona A, Bertolini G, Ricotta AM, et al. Variability of treatment duration for bacteraemia in the critically ill: a multinational survey. J Antimicrob Chemother. 2003;52(5):849-52.

295. Burnham JP, Olsen MA, Stwalley D, et al. Infectious Diseases Consultation Reduces 30-Day and 1-Year All-Cause Mortality for Multidrug-Resistant Organism Infections. Open Forum Infect Dis. 2018;5(3):ofy026.

296. Macheda G, Dyar OJ, Luc A, et al. Are infection specialists recommending short antibiotic treatment durations? An ESCMID international cross-sectional survey. J Antimicrob Chemother. 2018;73(4):1084-90.

297. Madaline T, Wadskier Montagne F, Eisenberg R, et al. Early Infectious Disease Consultation Is Associated With Lower Mortality in Patients With Severe Sepsis or Septic Shock Who Complete the 3-Hour Sepsis Treatment Bundle. Open Forum Infect Dis. 2019;6(10):ofz408.

298. Schmitt S, McQuillen DP, Nahass R, et al. Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. Clin Infect Dis. 2014;58(1):22-8.

299. Turner RB, Valcarlos E, Won R, et al. Impact of Infectious Diseases Consultation on Clinical Outcomes of Patients with Staphylococcus aureus Bacteremia in a Community Health System. Antimicrob Agents Chemother. 2016;60(10):5682-7.

300. Viale P, Tedeschi S, Scudeller L, et al. Infectious Diseases Team for the Early Management of Severe Sepsis and Septic Shock in the Emergency Department. Clin Infect Dis. 2017;65(8):1253-9.

301. Pugh R, Grant C, Cooke RP, et al. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015(8):CD007577.

302. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care. 2011;15(6):R267.

303. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, et al. Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis. Drugs. 2008;68(13):1841-54.

304. Tansarli GS, Andreatos N, Pliakos EE, et al. A Systematic Review and Meta-analysis of Antibiotic Treatment Duration for Bacteremia Due to Enterobacteriaceae. Antimicrob Agents Chemother. 2019;63(5).

305. Montravers P, Tubach F, Lescot T, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018;44(3):300-10.

306. Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intra-abdominal infections: evidence for the recommendations. Surg Infect (Larchmt). 2002;3(3):175-233.

307. van Engelen TSR, Wiersinga WJ, Scicluna BP, et al. Biomarkers in Sepsis. Crit Care Clin. 2018;34(1):139-52.

308. Annane D, Maxime V, Faller JP, et al. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. BMJ Open. 2013;3(2).

309. Bloos F, Trips E, Nierhaus A, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. JAMA Intern Med. 2016;176(9):1266-76.

310. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463-74.

311. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016;16(7):819-27.

312. Deliberato RO, Marra AR, Sanches PR, et al. Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. Diagn Microbiol Infect Dis. 2013;76(3):266-71.

313. Hochreiter M, Kohler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care. 2009;13(3):R83.

314. Liu BH, Li HF, Lei Y, et al. [Clinical significance of dynamic monitoring of procalcitonin in guiding the use of antibiotics in patients with sepsis in ICU]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013;25(11):690-3.

315. Nobre V, Harbarth S, Graf JD, et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med. 2008;177(5):498-505.

316. Oliveira CF, Botoni FA, Oliveira CR, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. Crit Care Med. 2013;41(10):2336-43.

317. Qu R, Ji Y, Ling Y, et al. Procalcitonin is a good tool to guide duration of antibiotic therapy in patients with severe acute pancreatitis. A randomized prospective single-center controlled trial. Saudi Med J. 2012;33(4):382-7.

318. Schroeder S, Hochreiter M, Koehler T, et al. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbecks Arch Surg. 2009;394(2):221-6.

319. Shehabi Y, Sterba M, Garrett PM, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014;190(10):1102-10.

320. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J. 2009;34(6):1364-75.

321. Xu XL, Yan FD, Yu JQ, et al. [Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment of sepsis patients]. Zhonghua Yi Xue Za Zhi. 2017;97(5):343-6.

322. Arulkumaran N, Khpal M, Tam K, et al. Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis. Crit Care Med. 2020;48(5):757-64.

323. Collins CD, Brockhaus K, Sim T, et al. Analysis to determine cost-effectiveness of procalcitonin-guided antibiotic use in adult patients with suspected bacterial infection and sepsis. Am J Health Syst Pharm. 2019;76(16):1219-25.

324. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8:CD000567.

325. Awad S, Allison SP, Lobo DN. The history of 0.9% saline. Clin Nutr. 2008;27(2):179-88.

326. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256(1):18-24.

327. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med. 2002;30(2):300-5.

328. Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest. 2006;130(4):962-7.

329. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg. 2001;93(4):817-22.

330. Williams EL, Hildebrand KL, McCormick SA, et al. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg. 1999;88(5):999-1003.

331. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347-55.

332. Young P, Bailey M, Beasley R, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA. 2015;314(16):1701-10.

333. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial. Am J Respir Crit Care Med. 2017;195(10):1362-72.

334. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378(9):829-39.

335. Brown RM, Wang L, Coston TD, et al. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med. 2019;200(12):1487-95.

336. Myburgh J. Patient-Centered Outcomes and Resuscitation Fluids. N Engl J Med. 2018;378(9):862-3.

337. Zampieri FG, Azevedo LCP, Correa TD, et al. Study protocol for the Balanced Solution versus Saline in Intensive Care Study (BaSICS): a factorial randomised trial. Crit Care Resusc. 2017;19(2):175-82.

338. Institute G. Plasma-Lyte 148® versUs Saline Study (PLUS). : ClinicalTrials.gov. ; 2020 [Available from: <https://clinicaltrials.gov/ct2/show/NCT02721654>. .

339. Caironi P, Tognoni G, Gattinoni L. Albumin replacement in severe sepsis or septic shock. N Engl J Med. 2014;371(1):84.

340. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis. J Crit Care. 2019;50:144-54.

341. Park CHL, de Almeida JP, de Oliveira GQ, et al. Lactated Ringer's Versus 4% Albumin on Lactated Ringer's in Early Sepsis Therapy in Cancer Patients: A Pilot Single-Center Randomized Trial. Crit Care Med. 2019;47(10):e798-e805.

342. Kakaei F HS, Asheghvatan A, Zarrintan S, Asvadi T, Beheshtirouy S, Mohajer A. Albumin As a Resuscitative Fluid in Patients with Severe Sepsis: A Randomized Clinical Trial. . Advances in Bioscience & Clinical Medicine. 2017;5(4):9 -16.

343. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ. 2013;346:f839.

344. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809-17.

345. Rochwerg B, Alhazzani W, Gibson A, et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. Intensive Care Med. 2015;41(9):1561-71.

346. Moeller C, Fleischmann C, Thomas-Rueddel D, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care. 2016;35:75-83.

347. Avni T, Lador A, Lev S, et al. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015;10(8):e0129305.

348. Regnier B, Safran D, Carlet J, et al. Comparative haemodynamic effects of dopamine and dobutamine in septic shock. Intensive Care Med. 1979;5(3):115-20.

349. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med. 2003;31(6):1659-67.

350. Cui J, Wei X, Lv H, et al. The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis. Ann Intensive Care. 2019;9(1):27.

351. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med. 2008;34(12):2226-34.

352. Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. Chest. 2001;120(3):989-1002.

353. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation. 1997;95(5):1122-5.

354. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18.

355. Dunser MW, Mayr AJ, Tur A, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med. 2003;31(5):1394-8.

356. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358(9):877-87.

357. Ukor IF, Walley KR. Vasopressin in Vasodilatory Shock. Crit Care Clin. 2019;35(2):247-61.

358. McIntyre WF, Um KJ, Alhazzani W, et al. Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. JAMA. 2018;319(18):1889-900.

359. Nagendran M, Russell JA, Walley KR, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. 2019;45(6):844-55.

360. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2016;2:CD003709.

361. Akinaga J, Lima V, Kiguti LR, et al. Differential phosphorylation, desensitization, and internalization of alpha1A-adrenoceptors activated by norepinephrine and oxymetazoline. Mol Pharmacol. 2013;83(4):870-81.

362. Belletti A, Benedetto U, Biondi-Zoccai G, et al. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. J Crit Care. 2017;37:91-8.

363. Russell JA, Vincent JL, Kjolbye AL, et al. Selepressin, a novel selective vasopressin V1A agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. Crit Care. 2017;21(1):213.

364. Laterre PF, Berry SM, Blemings A, et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. JAMA. 2019.

365. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care. 2014;18(5):534.

366. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med. 2017;377(5):419-30.

367. Liu ZM, Chen J, Kou Q, et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med. 2018;44(11):1816-25.

368. Walley KR. Sepsis-induced myocardial dysfunction. Curr Opin Crit Care. 2018;24(4):292-9.

369. Cunha-Goncalves D, Perez-de-Sa V, Larsson A, et al. Inotropic support during experimental endotoxemic shock: part II. A comparison of levosimendan with dobutamine. Anesth Analg. 2009;109(5):1576-83.

370. Dubin A, Lattanzio B, Gatti L. The spectrum of cardiovascular effects of dobutamine - from healthy subjects to septic shock patients. Rev Bras Ter Intensiva. 2017;29(4):490-8.

371. Wilkman E, Kaukonen KM, Pettila V, et al. Association between inotrope treatment and 90-day mortality in patients with septic shock. Acta Anaesthesiol Scand. 2013;57(4):431-42.

372. Dunser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. Intensive Care Med. 2012;38(4):557-74.

373. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. N Engl J Med. 2016;375(17):1638-48.

374. Bhattacharjee S, Soni KD, Maitra S, et al. Levosimendan does not provide mortality benefit over dobutamine in adult patients with septic shock: A meta-analysis of randomized controlled trials. J Clin Anesth. 2017;39:67-72.

375. Araghi A, Bander JJ, Guzman JA. Arterial blood pressure monitoring in overweight critically ill patients: invasive or noninvasive? Crit Care. 2006;10(2):R64.

376. Bur A, Hirschl MM, Herkner H, et al. Accuracy of oscillometric blood pressure measurement according to the relation between cuff size and upper-arm circumference in critically ill patients. Crit Care Med. 2000;28(2):371-6.

377. Kaur B, Kaur S, Yaddanapudi LN, et al. Comparison between invasive and noninvasive blood pressure measurements in critically ill patients receiving inotropes. Blood Press Monit. 2019;24(1):24-9.

378. Lehman LW, Saeed M, Talmor D, et al. Methods of blood pressure measurement in the ICU. Crit Care Med. 2013;41(1):34-40.

379. Riley LE, Chen GJ, Latham HE. Comparison of noninvasive blood pressure monitoring with invasive arterial pressure monitoring in medical ICU patients with septic shock. Blood Press Monit. 2017;22(4):202-7.

380. Vincent J. Arterial, Central Venous, and Pulmonary Artery Catheters In: JE P, editor. Critical care medicine : principles and diagnosis and management in the adult. 5th edition ed: Elsevier Philadelphia, PA; 2019. p. 40-9.

381. Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. Crit Care. 2002;6(3):199-204.

382. Bhattacharjee S, Maitra S, Baidya DK. Comparison between ultrasound guided technique and digital palpation technique for radial artery cannulation in adult patients: An updated meta-analysis of randomized controlled trials. J Clin Anesth. 2018;47:54-9.

383. Gu WJ, Wu XD, Wang F, et al. Ultrasound Guidance Facilitates Radial Artery Catheterization: A Meta-analysis With Trial Sequential Analysis of Randomized Controlled Trials. Chest. 2016;149(1):166-79.

384. O'Horo JC, Maki DG, Krupp AE, et al. Arterial catheters as a source of bloodstream infection: a systematic review and meta-analysis. Crit Care Med. 2014;42(6):1334-9.

385. Delaney A, Finnis M, Bellomo R, et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. Emerg Med Australas. 2020;32(2):210-9.

386. Ricard JD, Salomon L, Boyer A, et al. Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial. Crit Care Med. 2013;41(9):2108-15.

387. Cardenas-Garcia J, Schaub KF, Belchikov YG, et al. Safety of peripheral intravenous administration of vasoactive medication. J Hosp Med. 2015;10(9):581-5.

388. Tian DH, Smyth C, Keijzers G, et al. Safety of peripheral administration of vasopressor medications: A systematic review. Emerg Med Australas. 2020;32(2):220-7.

389. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care. 2015;30(3):653 e9-17.

390. Beck V, Chateau D, Bryson GL, et al. Timing of vasopressor initiation and mortality in septic shock: a cohort study. Crit Care. 2014;18(3):R97.

391. Black LP, Puskarich MA, Smotherman C, et al. Time to vasopressor initiation and organ failure progression in early septic shock. J Am Coll Emerg Physicians Open. 2020;1(3):222-30.

392. Edaigbini SA AM, Delia IZ, Ibrahim A, Okwunodulo O, Alegbejo-Olarinoye M. . Clinical competence with central venous lines by resident doctors in a Nigerian teaching hospital. Sub-Saharan Afr J Med 2017;4:47-51.

393. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.

394. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia. 2014;69(7):777-84.

395. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259-65.

396. Marik PE, Linde-Zwirble WT, Bittner EA, et al. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med. 2017;43(5):625-32.

397. Chen C, Kollef MH. Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study. Chest. 2015;148(6):1462-9.

398. Corl KA, Prodromou M, Merchant RC, et al. The Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): A Randomized Pilot Study. Crit Care Med. 2019;47(7):951-9.

399. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-705.

400. Macdonald SPJ, Keijzers G, Taylor DM, et al. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive Care Med. 2018;44(12):2070-8.

401. Semler MW, Janz DR, Casey JD, et al. Conservative Fluid Management After Sepsis Resuscitation: A Pilot Randomized Trial. J Intensive Care Med. 2019:885066618823183.

402. Meyhoff TS, Hjortrup PB, Moller MH, et al. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial-Protocol and statistical analysis plan. Acta Anaesthesiol Scand. 2019;63(9):1262-71.

403. Self WH, Semler MW, Bellomo R, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med. 2018;72(4):457-66.

404. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316(15):1583-9.

405. Investigators I-R, the A, New Zealand Intensive Care Society Clinical Trials G, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382(11):989-98.

406. Panwar R, Hardie M, Bellomo R, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. Am J Respir Crit Care Med. 2016;193(1):43-51.

407. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391(10131):1693-705.

408. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with sepsis: a post hoc analysis of data from the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). Intensive Care Med. 2020;46(1):17-26.

409. Barrot L, Asfar P, Mauny F, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. N Engl J Med. 2020;382(11):999-1008.

410. Mauri T, Turrini C, Eronia N, et al. Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. Am J Respir Crit Care Med. 2017;195(9):1207-15.

411. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-96.

412. Ni YN, Luo J, Yu H, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018;36(2):226-33.

413. Ou X, Hua Y, Liu J, et al. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. CMAJ. 2017;189(7):E260-E7.

414. Rochwerg B, Granton D, Wang DX, et al. High-flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: author's reply. Intensive Care Med. 2019;45(8):1171.

415. Demoule A, Chevret S, Carlucci A, et al. Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. Intensive Care Med. 2016;42(1):82-92.

416. Demoule A, Girou E, Richard JC, et al. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med. 2006;32(11):1756-65.

417. Bellani G, Laffey JG, Pham T, et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. Am J Respir Crit Care Med. 2017;195(1):67-77.

418. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998;339(7):429-35.

419. Honrubia T, Garcia Lopez FJ, Franco N, et al. Noninvasive vs conventional mechanical ventilation in acute respiratory failure: a multicenter, randomized controlled trial. Chest. 2005;128(6):3916-24.

420. BELENGUER-MUNCHARAZ A, CUBEDO-BORT M, BLASCO-ASENSIO D, et al. Non-invasive ventilation versus invasive mechanical ventilation in patients with hypoxemic acute respiratory failure in an Intensive Care Unit. A randomized controlled study. Minerva Pneumologica. 2017;56:1-10.

421. Tonelli R, Fantini R, Tabbi L, et al. Early Inspiratory Effort Assessment by Esophageal Manometry Predicts Noninvasive Ventilation Outcome in De Novo Respiratory Failure. A Pilot Study. Am J Respir Crit Care Med. 2020;202(4):558-67.

422. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818-24.

423. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-33.

424. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-8.

425. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-54.

426. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med. 1998;158(6):1831-8.

427. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999;27(8):1492-8.

428. Eichacker PQ, Gerstenberger EP, Banks SM, et al. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med. 2002;166(11):1510-4.

429. Marini JJ, Gattinoni L. Ventilatory management of acute respiratory distress syndrome: a consensus of two. Crit Care Med. 2004;32(1):250-5.

430. Tobin MJ. Culmination of an era in research on the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1360-1.

431. Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005;172(10):1241-5.

432. Checkley W, Brower R, Korpak A, et al. Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. Am J Respir Crit Care Med. 2008;177(11):1215-22.

433. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-55.

434. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019;9(1):69.

435. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med. 2016;42(12):1865-76.

436. Villar J, Martin-Rodriguez C, Dominguez-Berrot AM, et al. A Quantile Analysis of Plateau and Driving Pressures: Effects on Mortality in Patients With Acute Respiratory Distress Syndrome Receiving Lung-Protective Ventilation. Crit Care Med. 2017;45(5):843-50.

437. Hodgson CL, Cooper DJ, Arabi Y, et al. Maximal Recruitment Open Lung Ventilation in Acute Respiratory Distress Syndrome (PHARLAP). A Phase II, Multicenter Randomized Controlled Clinical Trial. Am J Respir Crit Care Med. 2019;200(11):1363-72.

438. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2017;318(14):1335-45.

439. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351(4):327-36.

440. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299(6):637-45.

441. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299(6):646-55.

442. Kacmarek RM, Villar J, Sulemanji D, et al. Open Lung Approach for the Acute Respiratory Distress Syndrome: A Pilot, Randomized Controlled Trial. Crit Care Med. 2016;44(1):32-42.

443. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303(9):865-73.

444. Goligher EC, Kavanagh BP, Rubenfeld GD, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. Am J Respir Crit Care Med. 2014;190(1):70-6.

445. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med. 1995;152(6 Pt 1):1835-46.

446. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354(17):1775-86.

447. Beitler JR, Sarge T, Banner-Goodspeed VM, et al. Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure-Guided Strategy vs an Empirical High PEEP-Fio2 Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2019;321(9):846-57.

448. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359(20):2095-104.

449. Turbil E, Galerneau LM, Terzi N, et al. Positive-end expiratory pressure titration and transpulmonary pressure: the EPVENT 2 trial. J Thorac Dis. 2019;11(Suppl 15):S2012-S7.

450. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308(16):1651-9.

451. Pipeling MR, Fan E. Therapies for Refractory Hypoxemia in Acute Respiratory Distress Syndrome. Jama-Journal of the American Medical Association. 2010;304(22):2521-7.

452. Cavalcanti AB, Suzumura É A, Laranjeira LN, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. Jama. 2017;318(14):1335-45.

453. Fan E, Wilcox ME, Brower RG, et al. Recruitment Maneuvers for Acute Lung Injury A Systematic Review. American Journal of Respiratory and Critical Care Medicine. 2008;178(11):1156-63.

454. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2017;14(Supplement\_4):S280-s8.

455. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010;36(4):585-99.

456. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-68.

457. Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. Crit Care Med. 1998;26(12):1977-85.

458. Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med. 1994;150(1):184-93.

459. Stocker R, Neff T, Stein S, et al. Prone postioning and low-volume pressure-limited ventilation improve survival in patients with severe ARDS. Chest. 1997;111(4):1008-17.

460. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med. 2001;345(8):568-73.

461. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. Jama. 2004;292(19):2379-87.

462. Klessig HT, Geiger HJ, Murray MJ, et al. A NATIONAL SURVEY ON THE PRACTICE PATTERNS OF ANESTHESIOLOGIST INTENSIVISTS IN THE USE OF MUSCLE-RELAXANTS. Critical Care Medicine. 1992;20(9):1341-5.

463. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Critical Care Medicine. 2002;30(1):142-56.

464. Hansenflaschen JH, Brazinsky S, Basile C, et al. USE OF SEDATING DRUGS AND NEUROMUSCULAR BLOCKING-AGENTS IN PATIENTS REQUIRING MECHANICAL VENTILATION FOR RESPIRATORY-FAILURE - A NATIONAL SURVEY. Jama-Journal of the American Medical Association. 1991;266(20):2870-5.

465. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med. 2006;34(11):2749-57.

466. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med. 2004;32(1):113-9.

467. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107-16.

468. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2013;17(2):R43.

469. Guervilly C, Bisbal M, Forel JM, et al. Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome. Intensive Care Med. 2017;43(3):408-18.

470. Lyu G, Wang X, Jiang W, et al. [Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014;26(5):325-9.

471. National Heart L, Blood Institute PCTN, Moss M, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N Engl J Med. 2019;380(21):1997-2008.

472. Alhazzani W, Belley-Cote E, Moller MH, et al. Neuromuscular blockade in patients with ARDS: a rapid practice guideline. Intensive Care Med. 2020.

473. Tarazan N, Alshehri M, Sharif S, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of randomized trials. Intensive Care Med Exp. 2020;8(1):61.

474. Johnson KL, Cheung RB, Johnson SB, et al. Therapeutic paralysis of critically ill trauma patients: perceptions of patients and their family members. American journal of critical care : an official publication, American Association of Critical-Care Nurses. 1999;8(1):490-8.

475. Munshi L, Walkey A, Goligher E, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(2):163-72.

476. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018;378(21):1965-75.

477. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351-63.

478. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. New England Journal of Medicine. 2018;378(9):809-18.

479. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-18.

480. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med. 2018;378(9):797-808.

481. Rygård SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2018;44(7):1003-16.

482. Dellinger RP, Bagshaw SM, Antonelli M, et al. Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial. JAMA. 2018;320(14):1455-63.

483. Zhou F, Peng Z, Murugan R, et al. Blood purification and mortality in sepsis: a meta-analysis of randomized trials. Crit Care Med. 2013;41(9):2209-20.

484. David S, Bode C, Putensen C, et al. Adjuvant therapeutic plasma exchange in septic shock. Intensive Care Med. 2021;47(3):352-4.

485. Hébert PC, Wells G, Blajchman MA, et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. New England Journal of Medicine. 1999;340(6):409-17.

486. Holst LB, Haase N, Wetterslev J, et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. New England Journal of Medicine. 2014;371(15):1381-91.

487. Hirano Y, Miyoshi Y, Kondo Y, et al. Liberal versus restrictive red blood cell transfusion strategy in sepsis or septic shock: a systematic review and meta-analysis of randomized trials. Crit Care. 2019;23(1):262.

488. Bergamin FS, Almeida JP, Landoni G, et al. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. Crit Care Med. 2017;45(5):766-73.

489. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13(3):260-8.

490. Madsen MB, Hjortrup PB, Hansen MB, et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial. Intensive Care Med. 2017;43(11):1585-93.

491. Welte T, Dellinger RP, Ebelt H, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). Intensive Care Med. 2018;44(4):438-48.

492. Alejandria MM, Lansang MA, Dans LF, et al. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database Syst Rev. 2013;2013(9):Cd001090.

493. Busani S, Damiani E, Cavazzuti I, et al. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. Minerva Anestesiol. 2016;82(5):559-72.

494. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med. 1994;330(6):377-81.

495. Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. New England Journal of Medicine. 2018;379(23):2199-208.

496. D'Silva KM, Mehta R, Mitchell M, et al. Proton pump inhibitor use and risk for recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Clin Microbiol Infect. 2021.

497. Granholm A, Zeng L, Dionne JC, et al. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. Intensive Care Med. 2019;45(10):1347-59.

498. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med. 2005;33(7):1565-71.

499. Alhazzani W, Lim W, Jaeschke RZ, et al. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013;41(9):2088-98.

500. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e195S-e226S.

501. Arabi YM, Al-Hameed F, Burns KEA, et al. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. New England Journal of Medicine. 2019;380(14):1305-15.

502. Kellum JA, Angus DC, Johnson JP, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med. 2002;28(1):29-37.

503. Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. Am J Kidney Dis. 2002;40(5):875-85.

504. Zha J, Li C, Cheng G, et al. The efficacy of renal replacement therapy strategies for septic-acute kidney injury: A PRISMA-compliant network meta-analysis. Medicine (Baltimore). 2019;98(16):e15257.

505. Zhao Y, Chen Y. Effect of renal replacement therapy modalities on renal recovery and mortality for acute kidney injury: A PRISMA-compliant systematic review and meta-analysis. Semin Dial. 2020;33(2):127-32.

506. Zarbock A, Kellum JA, Schmidt C, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. Jama. 2016;315(20):2190-9.

507. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. New England Journal of Medicine. 2016;375(2):122-33.

508. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. New England Journal of Medicine. 2018;379(15):1431-42.

509. Investigators S-A, Canadian Critical Care Trials G, Australian, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med. 2020;383(3):240-51.

510. Badawi O, Waite MD, Fuhrman SA, et al. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med. 2012;40(12):3180-8.

511. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36(11):3008-13.

512. Siegelaar SE, Hermanides J, Oudemans-van Straaten HM, et al. Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. Crit Care. 2010;14(6):R224.

513. 14. Diabetes Care in the Hospital: <em>Standards of Medical Care in Diabetes—2018</em>. Diabetes Care. 2018;41(Supplement 1):S144-S51.

514. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.

515. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125-39.

516. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35(10):1738-48.

517. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. Cmaj. 2009;180(8):821-7.

518. Song F, Zhong LJ, Han L, et al. Intensive insulin therapy for septic patients: a meta-analysis of randomized controlled trials. Biomed Res Int. 2014;2014:698265.

519. Intensive versus Conventional Glucose Control in Critically Ill Patients. New England Journal of Medicine. 2009;360(13):1283-97.

520. Yatabe T, Inoue S, Sakaguchi M, et al. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med. 2017;43(1):16-28.

521. Kuhn SO, Meissner K, Mayes LM, et al. Vitamin C in sepsis. Curr Opin Anaesthesiol. 2018;31(1):55-60.

522. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017;151(6):1229-38.

523. Putzu A, Daems AM, Lopez-Delgado JC, et al. The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients: A Systematic Review With Meta-Analysis of Randomized Controlled Trials. Crit Care Med. 2019;47(6):774-83.

524. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. Jama. 2019;322(13):1261-70.

525. Fujii T, Luethi N, Young PJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. Jama. 2020;323(5):423-31.

526. Moskowitz A, Huang DT, Hou PC, et al. Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial. JAMA. 2020;324(7):642-50.

527. Cooper DJ, Walley KR, Wiggs BR, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med. 1990;112(7):492-8.

528. Mathieu D, Neviere R, Billard V, et al. Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. Crit Care Med. 1991;19(11):1352-6.

529. Jaber S, Paugam C, Futier E, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 2018;392(10141):31-40.

530. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. Am J Surg. 2002;183(4):390-8.

531. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24(3):305-15.

532. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133-43.

533. Ibrahim EH, Mehringer L, Prentice D, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. JPEN J Parenter Enteral Nutr. 2002;26(3):174-81.

534. Malhotra A, Mathur AK, Gupta S. Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. J Postgrad Med. 2004;50(2):102-6.

535. Pupelis G, Austrums E, Jansone A, et al. Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. Eur J Surg. 2000;166(5):383-7.

536. Singh G, Ram RP, Khanna SK. Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. J Am Coll Surg. 1998;187(2):142-6.

537. Ely EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. Crit Care Med. 2017;45(2):321-30.

538. Brinkman-Stoppelenburg A, Rietjens JA, van der Heide A. The effects of advance care planning on end-of-life care: a systematic review. Palliat Med. 2014;28(8):1000-25.

539. White DB, Angus DC, Shields AM, et al. A Randomized Trial of a Family-Support Intervention in Intensive Care Units. N Engl J Med. 2018;378(25):2365-75.

540. Schneiderman LJ, Gilmer T, Teetzel HD. Impact of ethics consultations in the intensive care setting: a randomized, controlled trial. Crit Care Med. 2000;28(12):3920-4.

541. Schneiderman LJ, Gilmer T, Teetzel HD, et al. Effect of ethics consultations on nonbeneficial life-sustaining treatments in the intensive care setting: a randomized controlled trial. JAMA. 2003;290(9):1166-72.

542. Chen C, Michaels J, Meeker MA. Family outcomes and perceptions of end-of-life care in the intensive care unit: A mixed-methods review. J Palliat Care. 2019:825859719874767.

543. Andereck WS, McGaughey JW, Schneiderman LJ, et al. Seeking to reduce nonbeneficial treatment in the ICU: an exploratory trial of proactive ethics intervention. Crit Care Med. 2014;42(4):824-30.

544. Carson SS, Cox CE, Wallenstein S, et al. Effect of palliative care-led meetings for families of patients with chronic critical illness: A randomized clinical trial. JAMA. 2016;316(1):51-62.

545. Picker D, Dans M, Heard K, et al. A randomized trial of palliative care discussions linked to an automated early warning system alert. Crit Care Med. 2017;45(2):234-40.

546. Cheung W, Aggarwal G, Fugaccia E, et al. Palliative care teams in the intensive care unit: a randomised, controlled, feasibility study. Crit Care Resusc. 2010;12(1):28-35.

547. Curtis JR, Nielsen EL, Treece PD, et al. Effect of a quality-improvement intervention on end-of-life care in the intensive care unit: a randomized trial. Am J Respir Crit Care Med. 2011;183(3):348-55.

548. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. 2007;356(5):469-78.

549. Ma J, Chi S, Buettner B, et al. Early palliative care consultation in the medical ICU: A cluster randomized crossover trial. Crit Care Med. 2019;47(12):1707-15.

550. Clark E, MacCrosain A, Ward NS, et al. The key features and role of peer support within group self-management interventions for stroke? A systematic review. Disabil Rehabil. 2020;42(3):307-16.

551. Govindan S, Iwashyna TJ, Watson SR, et al. Issues of survivorship are rarely addressed during intensive care unit stays. Baseline results from a statewide quality improvement collaborative. Ann Am Thorac Soc. 2014;11(4):587-91.

552. Wobma R, Nijland RH, Ket JC, et al. Evidence for peer support in rehabilitation for individuals with acquired brain injury: A systematic review. J Rehabil Med. 2016;48(10):837-40.

553. McPeake J, Hirshberg EL, Christie LM, et al. Models of peer support to remediate post-intensive care xyndrome: A report developed by the Society of Critical Care Medicine Thrive International Peer Support Collaborative. Crit Care Med. 2019;47(1):e21-e7.

554. Mikkelsen ME, Jackson JC, Hopkins RO, et al. Peer support as a novel strategy to mitigate post-intensive care syndrome. AACN Adv Crit Care. 2016;27(2):221-9.

555. Halm MA. Effects of support groups on anxiety of family members during critical illness. Heart Lung. 1990;19(1):62-71.

556. Fridlund B, Stener-Bengtsson A, Wannman AL. Social support and social network after acute myocardial infarction; the critically ill male patient's needs, choice and motives. Intensive Crit Care Nurs. 1993;9(2):88-94.

557. McPeake J, Shaw M, Iwashyna TJ, et al. Intensive care syndrome:promoting independence and return to employment (InS:PIRE). Early evaluation of a complex intervention. PLoS One. 2017;12(11):e0188028.

558. Sabo KA, Kraay C, Rudy E, et al. ICU family support group sessions: family members' perceived benefits. Appl Nurs Res. 1989;2(2):82-9.

559. Parent N, Fortin F. A randomized, controlled trial of vicarious experience through peer support for male first-time cardiac surgery patients: impact on anxiety, self-efficacy expectation, and self-reported activity. Heart Lung. 2000;29(6):389-400.

560. Damianakis T, Tough A, Marziali E, et al. Therapy online: A web-based video support group for family caregivers of survivors with traumatic brain injury. J Head Trauma Rehabil. 2016;31(4):E12-20.

561. Harvey C, Dixon M, Padberg N. Support group for families of trauma patients: a unique approach. Crit Care Nurse. 1995;15(4):59-63.

562. Jones C, Macmillan RR, Griffiths RD. Providing psychological support for patients after critical illness. Clin Intensive Care. 1994;5(4):176-9.

563. Peskett M, Gibb P. Developing and setting up a patient and relatives intensive care support group. Nurs Crit Care. 2009;14(1):4-10.

564. Sacco TL, Stapleton MF, Ingersoll GL. Support groups facilitated by families of former patients: creating family-inclusive critical care units. Crit Care Nurse. 2009;29(3):36-45.

565. Haines KJ, Beesley SJ, Hopkins RO, et al. Peer Support in Critical Care: A Systematic Review. Crit Care Med. 2018;46(9):1522-31.

566. Danesh V. A prospective, 2-arm, single-blind, randomized controlled clinical feasibility trial design is planned. Forty CCI survivors will be randomized (1:1) to either the PS-PICS (peer support) intervention or usual care (control) group. NCT03788096 2019 [Available from: <https://clinicaltrials.gov/ct2/show/study/NCT03788096>.

567. Haines KJ HC, Cranwell K, Skinner EH Holton S, MacLeod-Smith B, Bates S, Iwashyna TJ, French C, Booth S, Carmody J. Development of a peer support model using experience-based co-design to improve critical care recovery. Critical care explorations. 2019;1(3):e0006.

568. Matthaeus-Kraemer CT, Thomas-Rueddel DO, Schwarzkopf D, et al. Crossing the handover chasm: Clinicians' perceptions of barriers to the early detection and timely management of severe sepsis and septic shock. J Crit Care. 2016;36:85-91.

569. Parent B, LaGrone LN, Albirair MT, et al. Effect of standardized handoff curriculum on improved clinician preparedness in the intensive care unit: A stepped-wedge cluster randomized clinical trial. JAMA Surg. 2018;153(5):464-70.

570. Nanchal R, Aebly B, Graves G, et al. Controlled trial to improve resident sign-out in a medical intensive care unit. BMJ Qual Saf. 2017;26(12):987-92.

571. Hess DR, Tokarczyk A, O'Malley M, et al. The value of adding a verbal report to written handoffs on early readmission following prolonged respiratory failure. Chest. 2010;138(6):1475-9.

572. Hoffman RL, Saucier J, Dasani S, et al. Development and implementation of a risk identification tool to facilitate critical care transitions for high-risk surgical patients. Int J Qual Health Care. 2017;29(3):412-9.

573. Chaboyer W, Lin F, Foster M, et al. Redesigning the ICU nursing discharge process: a quality improvement study. Worldviews Evid Based Nurs. 2012;9(1):40-8.

574. Medlock S, Eslami S, Askari M, et al. Improved communication in post-ICU care by improving writing of ICU discharge letters: a longitudinal before-after study. BMJ Qual Saf. 2011;20(11):967-73.

575. Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013;17(3):R100.

576. Donnelly JP, Lakkur S, Judd SE, et al. Association of Neighborhood Socioeconomic Status With Risk of Infection and Sepsis. Clin Infect Dis. 2018;66(12):1940-7.

577. Koch K, Norgaard M, Schonheyder HC, et al. Effect of socioeconomic status on mortality after bacteremia in working-age patients. A Danish population-based cohort study. PLoS One. 2013;8(7):e70082.

578. Ho KM, Dobb GJ, Knuiman M, et al. The effect of socioeconomic status on outcomes for seriously ill patients: a linked data cohort study. Med J Aust. 2008;189(1):26-30.

579. Ogundipe F, Kodadhala V, Ogundipe T, et al. Disparities in Sepsis Mortality by Region, Urbanization, and Race in the USA: a Multiple Cause of Death Analysis. J Racial Ethn Health Disparities. 2019;6(3):546-51.

580. Goodwin AJ, Nadig NR, McElligott JT, et al. Where you live matters: The impact of place of residence on severe sepsis incidence and mortality. Chest. 2016;150(4):829-36.

581. Prescott HC, Angus DC. Enhancing recovery from sepsis: A review. JAMA. 2018;319(1):62-75.

582. Gruther W, Pieber K, Steiner I, et al. Can early rehabilitation on the general ward after an intensive care unit stay reduce hospital length of stay in survivors of critical illness?: A randomized controlled trial. Am J Phys Med Rehabil. 2017;96(9):607-15.

583. Huang CY, Daniels R, Lembo A, et al. Life after sepsis: an international survey of survivors to understand the post-sepsis syndrome. Int J Qual Health Care. 2019;31(3):191-8.

584. Azoulay E, Pochard F, Chevret S, et al. Impact of a family information leaflet on effectiveness of information provided to family members of intensive care unit patients: a multicenter, prospective, randomized, controlled trial. Am J Respir Crit Care Med. 2002;165(4):438-42.

585. Bench S, Day T, Heelas K, et al. Evaluating the feasibility and effectiveness of a critical care discharge information pack for patients and their families: a pilot cluster randomised controlled trial. BMJ Open. 2015;5(11):e006852.

586. Demircelik MB, Cakmak M, Nazli Y, et al. Effects of multimedia nursing education on disease-related depression and anxiety in patients staying in a coronary intensive care unit. Appl Nurs Res. 2016;29:5-8.

587. Fleischer S, Berg A, Behrens J, et al. Does an additional structured information program during the intensive care unit stay reduce anxiety in ICU patients?: a multicenter randomized controlled trial. BMC Anesthesiol. 2014;14:48.

588. Gehrke-Beck S, Bänfer M, Schilling N, et al. The specific needs of patients following sepsis: a nested qualitative interview study. BJGP Open. 2017;1(1):bjgpopen17X100725.

589. Schmidt K, Worrack S, Von Korff M, et al. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: A randomized clinical trial. JAMA. 2016;315(24):2703-11.

590. Oermann MH, McInerney SM. An evaluation of sepsis Web sites for patient and family education. Plast Surg Nurs. 2007;27(4):192-6.

591. Légaré F, Adekpedjou R, Stacey D, et al. Interventions for increasing the use of shared decision making by healthcare professionals. Cochrane Database Syst Rev. 2018;7(7):Cd006732.

592. Anderson WG, Arnold RM, Angus DC, et al. Passive decision-making preference is associated with anxiety and depression in relatives of patients in the intensive care unit. J Crit Care. 2009;24(2):249-54.

593. Bokinskie JC. Family conferences: a method to diminish transfer anxiety. J Neurosci Nurs. 1992;24(3):129-33.

594. Choi J, Lingler JH, Donahoe MP, et al. Home discharge following critical illness: A qualitative analysis of family caregiver experience. Heart Lung. 2018;47(4):401-7.

595. Moss KO, Douglas SL, Baum E, et al. Family surrogate decision-making in chronic critical Illness: A qualitative analysis. Crit Care Nurse. 2019;39(3):e18-e26.

596. Austin CA, Mohottige D, Sudore RL, et al. Tools to Promote Shared Decision Making in Serious Illness: A Systematic Review. JAMA Intern Med. 2015;175(7):1213-21.

597. Bell CM, Brener SS, Gunraj N, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA. 2011;306:840-7.

598. Fabes J, Seligman W, Barrett C, et al. Does the implementation of a novel intensive care discharge risk score and nurse-led inpatient review tool improve outcome? A prospective cohort study in two intensive care units in the UK. BMJ Open. 2017;7(12):e018322.

599. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther. 2016;41(2):128-44.

600. Morandi A, Vasilevskis E, Pandharipande PP, et al. Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. J Am Geriatr Soc. 2013;61:1128-34.

601. Scales DC, Fischer HD, Li P, et al. Unintentional continuation of medications intended for acute illness after hospital discharge: A population-based cohort study. Journal of General Internal Medicine. 2016;31:196-202.

602. Stelfox HT, Bastos J, Niven DJ, et al. Critical care transition programs and the risk of readmission or death after discharge from ICU. Intensive Care Med. 2016;42(3):401-10.

603. Tomichek JE, Stollings JL, Pandharipande PP, et al. Antipsychotic prescribing patterns during and after critical illness: a prospective cohort study. Critical Care. 2016;20:378.

604. Ball C, Kirkby M, Williams S. Effect of the critical care outreach team on patient survival to discharge from hospital and readmission to critical care: non-randomised population based study. BMJ. 2003;327(7422):1014.

605. Baxter AD, Cardinal P, Hooper J, et al. Medical emergency teams at The Ottawa Hospital: the first two years. Can J Anaesth. 2008;55(4):223-31.

606. Choi S, Lee J, Shin Y, et al. Effects of a medical emergency team follow-up programme on patients discharged from the medical intensive care unit to the general ward: a single-centre experience. J Eval Clin Pract. 2016;22(3):356-62.

607. Elliott D, McKinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. Critical Care. 2011;15:R142.

608. Garcea G, Thomasset S, McClelland L, et al. Impact of a critical care outreach team on critical care readmissions and mortality. Acta Anaesthesiol Scand. 2004;48(9):1096-100.

609. Green A, Edmonds L. Bridging the gap between the intensive care unit and general wards-the ICU Liaison Nurse. Intensive Crit Care Nurs. 2004;20(3):133-43.

610. Leary T, Ridley S. Impact of an outreach team on re-admissions to a critical care unit. Anaesthesia. 2003;58(4):328-32.

611. Pittard AJ. Out of our reach? Assessing the impact of introducing a critical care outreach service. Anaesthesia. 2003;58(9):882-5.

612. Williams TA, Leslie G, Finn J, et al. Clinical effectiveness of a critical care nursing outreach service in facilitating discharge from the intensive care unit. Am J Crit Care. 2010;19(5):e63-72.

613. Pronovost P, Weast B, Schwarz M, et al. Medication reconciliation: a practical tool to reduce the risk of medication errors. J Crit Care. 2003;18(4):201-5.

614. Ravn-Nielsen LV, Duckert ML, Lund ML, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: A randomized clinical trial. JAMA Intern Med. 2018;178(3):375-82.

615. Taylor SP, Chou SH, Sierra MF, et al. Association between Adherence to Recommended Care and Outcomes for Adult Survivors of Sepsis. Ann Am Thorac Soc. 2020;17(1):89-97.

616. Etesse B, Jaber S, Mura T, et al. How the relationships between general practitioners and intensivists can be improved: the general practitioners' point of view. Crit Care. 2010;14(3):R112.

617. Kripalani S, LeFevre F, Phillips CO, et al. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA. 2007;297:831-41.

618. Robelia PM, Kashiwagi DT, Jenkins SM, et al. Information transfer and the hospital discharge summary: National primary care provider perspectives of challenges and opportunities. J Am Board Fam Med. 2017;30(6):758-65.

619. Weissman GE, Harhay MO, Lugo RM, et al. Natural language processing to assess documentation of features of critical illness in discharge documents of acute respiratory distress syndrome survivors. Ann Am Thorac Soc. 2016;13(9):1538-45.

620. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:502-9.

621. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304:1787-94.

622. Konig C, Matt B, Kortgen A, et al. What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. Qual Life Res. 2019;28(3):637-47.

623. Dietz BW, Jones TK, Small DS, et al. The relationship between index hospitalizations, sepsis, and death or transition to hospice care during 30-day hospital readmissions. Med Care. 2017;55(4):362-70.

624. Ortego A, Gaieski DF, Fuchs BD, et al. Hospital-based acute care use in survivors of septic shock. Crit Care Med. 2015;43(4):729-37.

625. Mayr FB, Talisa VB, Balakumar V, et al. Proportion and cost of unplanned 30-day readmissions after sepsis compared with other medical conditions. JAMA. 2017;317(5):530-1.

626. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. Jama. 2010;303(17):1716-22.

627. Field TS, Ogarek J, Garber L, et al. Association of early post-discharge follow-up by a primary care physician and 30-day rehospitalization among older adults. J Gen Intern Med. 2015;30(5):565-71.

628. Shen E, Koyama SY, Huynh DN, et al. Association of a dedicated post-hospital discharge follow-up visit and 30-Day readmission risk in a Medicare Advantage population. JAMA Intern Med. 2017;177(1):132-5.

629. Douglas SL, Daly BJ, Kelley CG, et al. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. Am J Crit Care. 2007;16(5):447-57.

630. Jónasdóttir RJ, Jónsdóttir H, Gudmundsdottir B, et al. Psychological recovery after intensive care: Outcomes of a long-term quasi-experimental study of structured nurse-led follow-up. Intensive Crit Care Nurs. 2018;44:59-66.

631. Kansagara D, Ramsay RS, Labby D, et al. Post-discharge intervention in vulnerable, chronically ill patients. J Hosp Med. 2012;7(2):124-30.

632. Deb P, Murtaugh CM, Bowles KH, et al. Does Early Follow-Up Improve the Outcomes of Sepsis Survivors Discharged to Home Health Care? Med Care. 2019;57(8):633-40.

633. Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med. 2015;3(1):61-9.

634. Jackson JC, Ely EW, Morey MC, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. Crit Care Med. 2012;40(4):1088-97.

635. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. Intensive Care Med. 2014;40(3):370-9.

636. Zhao J, Yao L, Li M, et al. [Effects of early intervention training on cognitive impairment in critical patients]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019;31(3):298-302.

637. Wong GKC, Mak JSY, Wong A, et al. Minimum clinically important difference of Montreal Cognitive Assessment in aneurysmal subarachnoid hemorrhage patients. J Clin Neurosci. 2017;46:41-4.

638. Teixeira C, Rosa RG. Post-intensive care outpatient clinic: is it feasible and effective? A literature review. Rev Bras Ter Intensiva. 2018;30(1):98-111.

639. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009;339:b3723.

640. Jensen JF, Egerod I, Bestle MH, et al. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multicenter randomized controlled trial, the RAPIT study. Intensive Care Med. 2016;42(11):1733-43.

641. Schofield-Robinson OJ, Lewis SR, Smith AF, et al. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. Cochrane Database Syst Rev. 2018;11:CD012701.

642. Kowalkowski M, Chou SH, McWilliams A, et al. Structured, proactive care coordination versus usual care for Improving Morbidity during Post-Acute Care Transitions for Sepsis (IMPACTS): a pragmatic, randomized controlled trial. Trials. 2019;20(1):660.

643. Paratz JD, Kenardy J, Mitchell G, et al. IMPOSE (IMProving Outcomes after Sepsis)-the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes-a double-blinded randomised controlled trial: protocol. BMJ Open. 2014;4(5):e004966.

644. Prescott HC, Iwashyna TJ, Blackwood B, et al. Understanding and enhancing sepsis survivorship.Priorities for research and practice. Am J Respir Crit Care Med. 2019;200(8):972-81.

645. Batterham AM, Bonner S, Wright J, et al. Effect of supervised aerobic exercise rehabilitation on physical fitness and quality-of-life in survivors of critical illness: an exploratory minimized controlled trial (PIX study). British journal of anaesthesia. 2014;113:130-7.

646. Battle C, James K, Temblett P, et al. Supervised exercise rehabilitation in survivors of critical illness: A randomised controlled trial. J Intensive Care Soc. 2019;20(1):18-26.

647. Connolly B, Thompson A, Douiri A, et al. Exercise-based rehabilitation after hospital discharge for survivors of critical illness with intensive care unit-acquired weakness: A pilot feasibility trial. J Crit Care. 2015;30(3):589-98.

648. Jones C, Skirrow P, Griffiths RD, et al. Rehabilitation after critical illness: A randomized, controlled trial. Critical Care Medicine. 2003;31:2456-61.

649. Jones TK, Fuchs BD, Small DS, et al. Post-Acute Care Use and Hospital Readmission after Sepsis. Ann Am Thorac Soc. 2015;12(6):904-13.

650. McDowell K, O'Neill B, Blackwood B, et al. Effectiveness of an exercise programme on physical function in patients discharged from hospital following critical illness: a randomised controlled trial (the REVIVE trial). Thorax. 2017;72(7):594-5.

651. McWilliams DJ, Benington S, Atkinson D. Outpatient-based physical rehabilitation for survivors of prolonged critical illness: A randomized controlled trial. Physiother Theory Pract. 2016;32(3):179-90.

652. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: The RECOVER randomized clinical trial. JAMA internal medicine. 2015;175:901-10.

653. Health NIf, Excellence C. Rehabilitation after critical illness in adults: NICE Reino Unido; 2014 [Available from: <https://www.nice.org.uk/guidance/qs158/resources/rehabilitation-after-critical-illness-in-adults-pdf-75545546693317>.

654. Major ME, Kwakman R, Kho ME, et al. Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge. Critical Care (London, England). 2016;20:354.