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# What is new and different in the 2021 Surviving Sepsis Campaign guidelines

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## Abstract

The Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Sepsis and Septic Shock provide recommendations on the care of hospitalized adult patients with (or at risk for) sepsis. This review discusses what is new or different in the 2021 SSC adult sepsis guidelines compared to 2016. The guidelines include new weak recommendations for use of balanced fluid over saline 0.9%, use of intravenous corticosteroids for septic shock when there is ongoing vasopressor requirement, and peripheral initiation of intravenous vasopressors over delaying initiation in order to obtain central venous access. As before, there is a strong recommendation to initiate antimicrobials within 1 h of sepsis and septic shock, but there are now additional recommendations when the diagnosis is uncertain. The recommendation for initial fluid resuscitation in septic shock of 30 mL/kg crystalloid has been downgraded from strong to weak. Finally, there are 12 new recommendations addressing long-term outcomes from sepsis, including strong recommendations to screen for economic and social support and to make referrals for follow-up where available; use shared decision-making in post-intensive care unit (ICU) and hospital discharge planning; reconcile medications at both ICU and hospital discharge; provide information about sepsis and its sequelae in written and verbal hospital discharge summary; and to provide assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.

### Keywords

Septic shock · Resuscitation · Antimicrobial agents · Critical care · Discharge planning

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## Introduction

The Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Sepsis and Septic Shock provide guidance on the care of hospitalized adult patients with (or at risk for) sepsis [1, 2]. The first SSC guidelines were published in 2004, with subsequent updates published in 2008, 2012, 2016, and 2021, as well as separate guidelines for pediatric sepsis and coronavirus disease 2019 (COVID-19)

in 2020. The 2021 adult sepsis guideline panel included 60 multiprofessional expert clinicians and methodologists from 22 countries, as well as 11 members of the public representing patients and families. The guidelines were endorsed by 24 professional organizations. This review discusses what is new or different in the 2021 SSC adult sepsis guidelines compared to 2016.



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## Scope and methods

The 2021 guidelines are based on literature published until July 2019. They contain a new section focused on long-term outcomes and recovery from sepsis. This new section was added because an estimated 38 million people survive sepsis each year [3], many of whom experience poor longer-term outcomes [4], and the 2017 World Health Organization resolution on sepsis called for better support of sepsis survivors [5]. In Germany, sepsis remains not only a significant cause of hospital admission and mortality [6], but also of long-term physical and psychological morbidity [7, 8].

To make space for recommendations related to longer-term outcomes and recovery from sepsis, other sections of the guidelines were shortened. Specifically, the number of recommendations related to adjunctive or supportive care (e.g., nutrition, blood product transfusion, anticoagulation, renal replacement therapy, stress ulcer prophylaxis, and sedation) were reduced. The rationale for this change was that many of these recommendations were not specific to sepsis, and are covered in other guidelines addressing the care of hospitalized or critically ill patients.

New to the 2021 Guidelines, recommendations were formulated using the evidence-to-decision (EtD) framework, which takes into account not only the magnitude of effect and quality of evidence, but also patient values, resources required, equity, acceptability, and feasibility [9]. Based on the EtD framework, recommendations are more likely to be weak (“we suggest”) than strong (“we recommend”) when there is low certainty of evidence, close balance between desirable and undesirable effects, or substantial resources are required for the intervention.

## Recommendations

The 2021 Guidelines have 93 statements, including 54 weak recommendations, 15 strong recommendations, 15 best practice statements, and 9 statements of no recommendation. In the following, we highlight a subset of statements that are new or revised since 2016.

### qSOFA as a single screening tool for sepsis

qSOFA (a three-point tool incorporating altered mentation, elevated respiratory rate, and systolic blood pressure  $\leq 100$  mm Hg) was introduced in 2016 to facilitate rapid risk-stratification of patients with suspected or proven infection [10]. However, there has been confusion about the goal of qSOFA and how to incorporate it into practice [11]. While qSOFA provides prognostic information, it is neither sensitive nor specific for sepsis [12]. As such, the guidelines now include a strong recommendation against using qSOFA as a single screening tool for sepsis.

### 30 ml/kg initial fluid bolus

The guidelines suggest delivering 30 ml/kg intravenous crystalloid fluid for patients with sepsis-induced hypotension or septic shock. The average volume of fluid received prerandomization in the PROCESS [13], PROMISE [14], and ARISE [15] trials was in the range of 30 ml/kg, suggesting that most patients with sepsis-induced hypotension need at least this volume of fluid [16]. Furthermore, in a multicenter observational study, implementation of a sepsis treatment bundle including a 30 ml/kg fluid bolus was associated with increased fluid administration and improved mortality, particularly among patients with heart failure and/or kidney disease [17]. However, there are no prospective trials comparing different fluid volumes for initial resuscitation in sepsis. Overall, based on limitations of the evidence, the panel downgraded 30 ml/kg resuscitation volume from a strong recommendation to a weak recommendation.

### Ongoing resuscitation

The 2021 guidelines include a statement of “no recommendation” for using a fluid-liberal versus fluid-restrictive resuscitation strategy among patients with ongoing signs of hypoperfusion after the initial 30 ml/kg crystalloid fluid bolus. While five pilot trials were identified comparing fluid-liberal versus fluid-restrictive resuscitation strategies, they were small and used variable methods to promote liberal

versus restrictive fluid strategies. Thus, despite these studies, there was insufficient evidence to make a recommendation. Several trials are ongoing to address this question (NCT03668236; NCT03434028).

### Capillary refill time as an adjunct measure for guiding resuscitation

As in 2016, the guidelines suggest targeting resuscitation to decrease serum lactate when elevated, over not using serum lactate. New to the 2021 guideline, however, there is also a suggestion to use capillary refill time as an adjunct to other measures of perfusion to guide resuscitation. This weak recommendation was informed by the ANDROMEDA-SHOCK trial, in which patients randomized to a resuscitation strategy guided by capillary refill time versus lactate had similar 28-day mortality (34.9% vs 43.4%,  $p = 0.06$ ) [18].

### Antimicrobial timing recommendations incorporate diagnostic certainty and illness severity

As in 2016, the 2021 guidelines strongly recommend administration of antimicrobials as soon as possible, ideally within 1 h, for patients with sepsis and septic shock. However, recognizing that sepsis diagnosis is often uncertain in practice [19–21], the 2021 guidelines include additional recommendations for antimicrobial timing when sepsis is possible (■ Table 1). For patients without shock, the guideline recommends a rapid assessment of infectious versus noninfectious causes of illness, and administration of antimicrobials within 3 h if concern for infection persists. However, for patients with shock, the guidelines recommend administration of antimicrobials immediately—recognizing that the risk of delaying antimicrobials is greater among patients with septic shock [22, 23]. These new recommendations for possible sepsis, which are stratified by presence of shock, acknowledge the urgency of antimicrobial treatment for sepsis while also trying to avoid indiscriminate antimicrobial use by encouraging a rapid evaluation prior to treatment among patients without shock.

Table 1 The 2021 Surviving Sepsis Campaign (SSC) recommendations on timing of first antimicrobial administration		
	Shock is present	Shock is absent
Sepsis is definite or probable	For adults with possible septic shock or a high likelihood of sepsis, we <b>recommend</b> administering antimicrobials immediately, ideally within 1 h of recognition	For adults with possible sepsis without shock, we <b>recommend</b> administering antimicrobials immediately, ideally
Sepsis is possible	For adults with possible septic shock or a high likelihood of sepsis, we <b>recommend</b> administering antimicrobials immediately, ideally within 1 h of recognition	For adults with possible sepsis without shock, we <b>recommend</b> a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognized
Infection is unlikely	–	For adults with a low likelihood of infection and without shock, we <b>suggest</b> deferring antimicrobials while continuing to closely monitor the patient

### Balanced fluids over saline 0.9%

New in 2021, the guideline suggests using balanced fluids over saline 0.9%. This recommendation is informed by a network meta-analysis [24] and the cluster-randomized SMART trial [25]. Among the prespecified subgroup with sepsis in SMART, 30-day mortality was lower in patients randomized to balanced fluid versus saline (odds ratio [OR] 0.90, 95% confidence interval [CI] 0.67, 0.94) [26]. Since the 2021 guideline recommendations were finalized, the BaSICS trial examining balanced fluids (Plasma-Lyte-148) versus saline was published [27], and will need to be incorporated into future meta-analyses. Among patients with sepsis, 90-day mortality was similar among those randomized to balanced fluid versus saline (46.7% vs 49.0%) [27]. Also, in contrast to the SMART trial, there was no significant difference in the development of moderate to severe acute kidney injury. However, the majority of patients received non-study fluid prior to intensive care unit (ICU) admission and enrollment into the trial.

### Other fluids

As in prior years, the 2021 guidelines recommend crystalloids as first-line fluid for resuscitation; recommend against use of starches for resuscitation; suggest against use of gelatins due to inconclusive effect on mortality but increased adverse effects and increased costs; and suggest using albumin among patients who received large volumes of crystalloid (over using crystalloid alone). However, due to limited data, the guidelines do not provide a specific threshold of crystalloid fluid volume above which albumin should be considered.

### Peripheral vasopressor initiation

New in 2021, the guidelines suggest starting vasopressors peripherally over delaying initiation until central venous access is secured. This recommendation is based on mounting evidence that peripheral administration of intravenous vasopressors is safe, particularly if infused proximally and for short periods of time (<6 h) [28, 29]. Furthermore, peripheral initiation of vasopressors is associated with shorter time to administration and faster time to achieving goal blood pressure [30].

### Corticosteroids for septic shock

The 2016 guidelines suggested against using intravenous (IV) hydrocortisone to treat septic shock patients if fluid resuscitation and vasopressor therapy were able to restore hemodynamic stability. The 2021 guidelines now suggest using IV corticosteroids for adults with septic shock who have an ongoing vasopressor requirement. The revised recommendation takes into account several randomized controlled trials (RCTs) [31–33] and updated meta-analyses [34, 35], in which corticosteroid therapy was found to shorten the duration of shock but have unclear effect on mortality. The panel judged the desirable effects of shock resolution to outweigh the undesirable effects of corticosteroid therapy and supported a weak recommendation in favor of using low-dose corticosteroid therapy in septic shock.

### Vitamin C for septic shock

The 2021 guidelines suggest against using IV vitamin C for septic shock. The panel completed a meta-analysis of available RCTs, and the balance of effects was

judged to favor neither vitamin C nor comparator. In the absence of a benefit, the panel suggested against use.

### Long-term outcomes and recovery from sepsis

The 2021 guidelines include 12 new recommendations addressing the long-term outcome and recovery from sepsis (Table 2). These include strong recommendations to screen for economic and social support and make referrals for follow-up where available; use shared decision-making in post-ICU and hospital discharge planning; reconcile medications at both ICU and hospital discharge; provide information about sepsis and its sequelae in written and verbal hospital discharge summary; and to provide assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge. While some might argue that these recommendations are common sense, the available data suggest that implementation into practice has lagged [36, 37]. There was insufficient evidence to make recommendations regarding timing of outpatient follow-up or provision of early cognitive therapy.

### Conclusion

The 2021 Surviving Sepsis Campaign (SSC) guidelines include several new or revised recommendations on early sepsis management, as well as a new set of recommendations on peri-discharge management to enhance long-term outcomes from sepsis. There were several important aspects of management for which the panel could not provide a recommendation (e.g., ongoing fluid management strategy and early cognitive rehabilitation), underscoring the

Table 2 New recommendations addressing long-term outcomes and recovery from sepsis	
Strength	Recommendation
Strong	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
	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
	For adults with sepsis and septic shock, we recommend reconciling medications at both ICU and hospital discharge
	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 post-ICU/post-sepsis syndrome in the written and verbal hospital discharge summary
	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
	For adult survivors of sepsis or septic shock, we recommend assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge
Weak	For adult survivors of sepsis or septic shock and their families, we suggest referral to peer support groups over no such referral
	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
	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
	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 ward
	For adult survivors of sepsis or septic shock, we suggest referral to a post-critical illness follow-up program if available
	For adult survivors of sepsis or septic shock receiving mechanical ventilation for > 48 h or an ICU stay of > 72 h, we suggest referral to a post-hospital rehabilitation program

ICU intensive care unit

need for further research to guide care for sepsis [38–40].

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**Declarations**

**Conflict of interest.** H.C. Prescott and M. Ostermann declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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## Was ist neu und was ist anders in den SSC(Surviving Sepsis Campaign)-Leitlinien

Die internationalen Leitlinien der Surviving Sepsis Campaign (SSC) für die Behandlung von Sepsis und septischem Schock enthalten Empfehlungen für die Versorgung von erwachsenen Patienten mit Sepsis (bzw. mit Sepsisrisiko) im Krankenhaus. In dieser Übersicht wird erläutert, was in den 2021 erarbeiteten SSC-Leitlinien für Sepsis bei Erwachsenen im Vergleich zu 2016 neu bzw. anders ist. Die Leitlinien enthalten neue schwache Empfehlungen für die Verwendung von balancierter Flüssigkeit anstelle von 0,9%iger Natriumchloridlösung, für den Einsatz intravenöser Kortikosteroide bei septischem Schock, wenn ein anhaltender Bedarf für Vasopressoren besteht, und dafür, intravenöse Vasopressoren schon peripher einzuleiten, statt erst verzögert, wenn ein zentralvenöser Zugang besteht. Nach wie vor wird dringend empfohlen, bei Sepsis und septischem Schock innerhalb von einer Stunde mit einer antimikrobiellen Therapie zu beginnen, doch gibt es nun zusätzliche Empfehlungen, wenn die Diagnose nicht sicher ist. Die Empfehlung für eine initiale Flüssigkeitszufuhr bei septischem Schock von 30 ml/kg Kristalloid wurde von stark auf schwach herabgestuft. Schließlich gibt es 12 neue Empfehlungen, die sich mit den Langzeitfolgen der Sepsis befassen, darunter die nachdrücklichen Empfehlungen, hinsichtlich finanzieller und sozialer Unterstützung zu screenen und, falls verfügbar, zur Nachsorge zu überweisen, bei der Planung der Verlegung von der Intensivstation (ICU) und der Entlassung aus der stationären Behandlung die gemeinsame Entscheidungsfindung zu nutzen, die Medikation sowohl auf der ICU als auch bei der Krankenhausentlassung abzustimmen, Informationen über die Sepsis und ihre Folgen in der schriftlichen und mündlichen Zusammenfassung der Entlassung aus dem Krankenhaus bereitzustellen und nach der Entlassung aus dem Krankenhaus ein Assessment der und eine Nachsorge für körperliche, kognitive und emotionale Probleme zu anbieten.

### Schlüsselwörter

Septischer Schock · Reanimation · Antimikrobielle Substanzen · Intensivversorgung · Entlassmanagement

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