# International guidelines for the management of sepsis and septic shock: 2021

Surviving Sepsis Campaign

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# COI Disclosure

- Co-chair SSC Adult Sepsis Guidelines, Member SSC Steering Committee, Co-chair SSC COVID-19 Management Guidelines, Member NIH COVID-19 management guidelines



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- All panelists
- Public members
- Ms. Lori Harmon and Ms. Julie Higham




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# Surviving Sepsis Campaign Timeline

**2002**

**Declaration Barcelona**

2002 SSC initated between ESICM, SCCM & ISF

**2004 Adult Guidelines**

2005 working with IHI to create first set of performance improvement bundles.
2008 SSC independent of industry funding and ISF no longer a partner

**2006**

**2008 Adult Guidelines**

2010 Data published on 15,000 patients from SSC database demonstrating 20% RRR for death.
2013 sepsis metrics adopted by New York state, USA.

**2010**

**2012 Adult Guidelines**

2014 Data published on 30,000 patients from SSC database demonstrating 25% RRR for death.

**2014**

**2016 Adult Guidelines**

2017 Data from New York state published on 100,000 patients with 15.2% RRR for death.
2018 Hour-one bundle released.

**2018**

**2021 Adult Guidelines**

2018 Sepsis research priorities published
2020 SSC COVID-19 Guidelines

**2022**



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# Guideline Development Process

## 1. Panel Constitution

1. Development of collaboration
2. Agreement of budget from funding societies
3. Identify methodologists and librarians
4. Identify panel members ensuring diversity
5. Review of potential conflicts of interest

## 2. Evaluation of Evidence

1. Survey of current practice
2. Development of PICO questions
3. Prioritization of outcomes
4. Literature search
5. Systematic review & Meta-analysis
6. Development of evidence profiles
7. Grading of evidence

## 3. Developing Recommendations

1. Rigorous management of conflicts of interest
2. Completion of Evidence to Decision framework
3. Grading & Drafting of recommendations
4. Panel voting on recommendations
5. Consensus agreement of recommendations

## 4. Completion of Guidelines

1. Drafting of manuscript
2. Peer review by collaboration and journals
3. Publish manuscript
4. Disseminate findings
5. Implementation of recommendations



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# SSC Guidelines Panel Composition

## PANEL MAKE UP

**29** Subject Matter Experts

**24** Society representatives

**7** Methodologists

**6** Lay Members

## GENDER BALANCE

**37** Male

**16** Female

## GEOGRAPHY

**5** Africa / Middle East

**5** Asia

**10** Europe

**25** North America

**4** Oceania

**4** South America

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# SSC Adult Sepsis Guidelines Panel Members

Laura Evans: Co-chair
Andrew Rhodes: Co-chair
Waleed Alhazzani: Methodology chair
Massimo Antonelli: COI co-chair
Craig M. Coopersmith: COI co-chair
Craig French: Group lead
Flavia R. Machado: Group lead
Lauralyn Mcintyre: Group lead
Marlies Ostermann: Co-vice-chair
Hallie C. Prescott: Co-vice-chair
Christa Schorr: Group lead
Steven Simpson: Group lead
W. Joost Wiersinga
Fayez Alshamsi
Derek C. Angus
Yaseen Arabi
Luciano Azevedo
Richard Beale
Gregory Beilman
Emilie Belley-Cote
Lisa Burry
Maurizio Cecconi
John Centofanti
Angel Coz Yataco
Jan De Waele
R. Phillip Dellinger
Kent Doi
Bin Du
Elisa Estenssoro
Ricard Ferrer
Charles Gomersall
Carol Hodgson
Morten Hylander Moller
Theodore Iwashyna
Shevin Jacob
Ruth Kleinpell
Michael Klompas
Younsuck Koh
Anand Kumar
Arthur Kwizera
Suzana Lobo
Henry Masur
Steven McGloughlin
Sangeeta Mehta
Yatin Mehta
Mervyn Mer
Mark Nunnally
Simon Oczkowski
Tiffany Osborn
Elizabeth Papathanassoglou
Anders Perner
Michael Puskarich
Jason Roberts
William Schweickert
Maureen Seckel
Jonathan Sevransky
Charles L. Sprung
Tobias Welte
Janice Zimmerman
Mitchell Levy: Group Lead



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# Management of potential COI

- Direct financial and industry-related COIs were not permitted.
- Intellectual COI: leading clinical trial(s) relevant to the recommendation
- Panel members were not allowed to vote on recommendations with a potential intellectual COI



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# Prioritization of Questions

We used a systematic approach to select and prioritize topics for adult guidelines.

Our approach incorporated

1) **Practice variability** based on the international survey results (**clinical equipoise**),
2) **Panel member's assessment** of question importance (**experts input**),
3) Inclusion in previous iterations of the guideline (**evidence gap**).

The final decision was achieved by discussion and consensus between panellists in each group, and the SSC leadership approved final list of PICO questions.

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# Implications of recommendations

| | Strong Recommendation | Weak Recommendation |
|---|---|---|
| **For Patients** | **Most** individuals in this situation would want the recommended course of action, and only a **small** proportion would not | The **majority** of individuals in this situation would want the suggested course of action, but **many** would not |
| **For Clinicians** | **Most** individuals **should receive** the recommended course of action.<br><br>Formal decision aids **are not likely to be needed** to help individuals make decisions consistent with their values and preferences | Different choices are likely to be appropriate for different patients<br><br>Therapy should be tailored to the individual patient's circumstances, such as patients' or family's values and preferences |
| **For Policymakers** | Can be adapted as policy in most situations, including for use as performance indicators | Policies will likely be variable |

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# What is different about the 2021 guidelines?

- ✓ Greater emphasis on panel diversity- gender, geographic & economic.
- ✓ Questions selected following international evaluation of practice and uncertainties.
- ✓ PICO questions about long term outcomes after sepsis added
- ✓ Use of ‘Evidence to Decision’ framework as a transparent and structured system for formulating recommendations.

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# What is new in the 2021 guidelines recommendations?
# A few highlights



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# Screening for sepsis

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In acutely ill patients should we use qSOFA criteria to screen for the presence of sepsis? | **We recommend against using qSOFA compared with SIRS, NEWS, or MEWS as a single-screening tool for sepsis or septic shock.** | Strong, moderate-quality evidence | New recommendation |

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# A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality

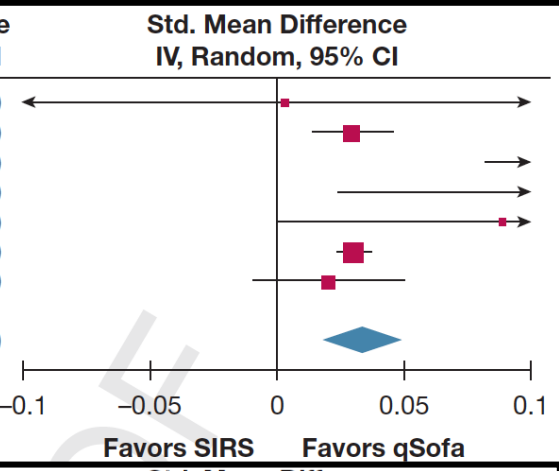
## A Systematic Review and Meta-Analysis

orge Salluh, MD, PhD; and Pedro Póvoa, MD, PhD

| Study or Subgroup | qSOFA Mean | qSOFA SD | qSOFA Total | SIRS Mean | SIRS SD | SIRS Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| April, 2017 | 0.66 | 2.61 | 214 | 0.65 | 2.61 | 214 | 0.7% | 0.00 (–0.19 to 0.19) |
| Churpek, 2017 | 0.69 | 1.34 | 30,677 | 0.65 | 1.34 | 30,677 | 31.9% | 0.03 (0.01 to 0.05) |
| Finkelsztein, 2017 | 0.74 | 0.47 | 152 | 0.59 | 0.5 | 152 | 0.5% | 0.31 (0.08 to 0.53) |
| Freund, 2017 | 0.8 | 1.59 | 879 | 0.65 | 0.83 | 879 | 2.8% | 0.12 (0.02 to 0.21) |
| Park, 2017 | 0.733 | 1.54 | 1,009 | 0.599 | 1.46 | 1,009 | 3.2% | 0.09 (0.00 to 0.18) |
| Raith, 2017 | 0.607 | 0.88 | 184,875 | 0.58 | 0.88 | 184,875 | 42.6% | 0.03 (0.02 to 0.04) |
| Williams, 2017 | 0.73 | 0.48 | 8,871 | 0.72 | 0.48 | 8,871 | 18.3% | 0.02 (–0.01 to 0.05) |
| **Total (95% CI)** | | | **226,677** | | | **226,677** | **100.0%** | **0.03 (0.02 to 0.05)** |

Heterogeneity: Tau² = 0.00; Chi² = 11.39, df = 6 (*P* = .08); I² = 47%
Test for overall effect: Z = 4.12 (*P* < .0001)

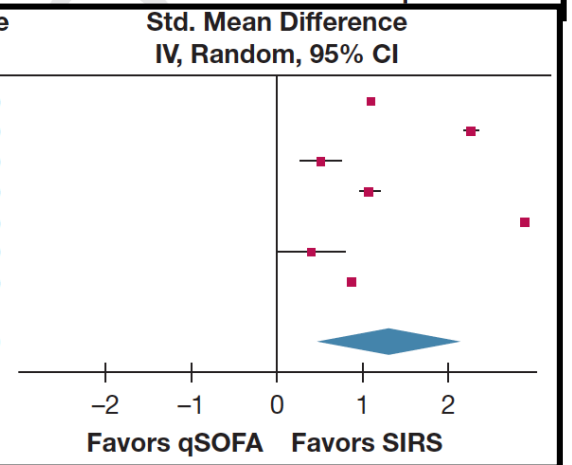
Mortality




| Study or Subgroup | SIRS Mean | SIRS SD | SIRS Total | qSOFA Mean | qSOFA SD | qSOFA Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Churpek, 2017 | 0.88 | 0.45 | 30,677 | 0.38 | 0.45 | 30,677 | 14.4% | 1.11 (1.09 to 1.13) |
| Donnelly, 2017 | 0.54 | 0.02 | 2,593 | 0.12 | 0.26 | 2,593 | 14.3% | 2.28 (2.21 to 2.35) |
| Dorsett, 2017 | 0.39 | 0.5 | 152 | 0.16 | 0.38 | 152 | 14.2% | 0.52 (0.29 to 0.75) |
| Freund, 2017 | 0.74 | 0.45 | 879 | 0.25 | 0.45 | 879 | 14.3% | 1.09 (0.99 to 1.19) |
| Raith, 2017 | 0.86 | 0.11 | 184,875 | 0.54 | 0.11 | 184,875 | 14.4% | 2.91 (2.90 to 2.92) |
| Siddiqui, 2017 | 0.62 | 0.47 | 58 | 0.42 | 0.51 | 58 | 14.0% | 0.41 (0.04 to 0.77) |
| Williams, 2017 | 0.47 | 0.48 | 8,871 | 0.1 | 0.34 | 8,871 | 14.4% | 0.89 (0.86 to 0.92) |
| **Total (95% CI)** | | | **228,105** | | | **228,105** | **100.0%** | **1.32 (0.40 to 2.24)** |

Heterogeneity: Tau² = 1.53; Chi² = 43948.08, df = 6 (*P* < .00001); I² = 100%
Test for overall effect: Z = 2.81 (*P* = .005)

Sepsis



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# Initial Resuscitation

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In patients with known or suspected infection and hypotension and / or an elevated lactate should we administer 30mL/Kg BW of crystalloids or a rapid small volume fluid challenge and re-assess? | **For patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hr of resuscitation.** | Weak, low quality of evidence | Downgraded from Strong, low quality of evidence "We recommend that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hr" |

SYSTEMATIC REVIEW ARTICLE

## Use of the Fluid Challenge in Critically Ill Adult Patients: A Systematic Review

Antonio Messina, MD, PhD,* Federico Longhini, MD,† Corinne Coppo, MD,‡ Alice Pagni, MD,† Ramona Lunga, MD,‖ Chiara Ronco, MD,‡ Marco Ambrogio Cattaneo, MD,† Simone Dore, PhD,§ Giovanni Sotgiu, MD,§ and Paolo Navalesi, MD, FERS‖

The fluid challenge (FC) aims at identifying patients in whom fluid administration improves hemodynamics. Although the FC has been extensively studied, the implementation and definition of responsiveness are not standardized. This systematic review of studies published between January 1, 1994 and December 31, 2016 characterizes these key components of the FC for critically ill adult patients, as described in the medical literature in the last 20 years. A literature search was performed using MEDLINE, Embase, and Cochrane. For each study, data were collected on study design, study size, study setting, patient population, and how the FC was administered. Eligibility criteria for FC were (1) the infusion of a definite quantity of fluid, (2) of a specific type, (3) in a fixed time period (expressed as either span or infusion rate), (4) with a defined hemodynamic variable as the target, and (5) for a predetermined threshold. One hundred fifty-seven full-text manuscripts were extracted from 878 potentially relevant studies. The indication criteria were met by 71 studies including 3617 patients. Sixty-six studies were from a single center and 45 were prospective observational in format. The most commonly assessed infused was 500 mL over by 55 (77.5%) studies. The most commonly infused fluids were colloids (62.0%). In 43 (60.6%) studies, the FC was administered between 20 and 30 minutes. A positive response to fluid administration was defined as an increase ≥15% of cardiac index or cardiac output in 44 (62.0%) studies. Static or dynamic physiologic indices were utilized in a minority of studies (36.9%) and widely lacks for interrupting the FC are adopted in 8 (8.8%) studies only. This systematic review indicates that the FC most commonly consists in infusing 500 mL of crystalloids or colloids in 20–30 minutes, and considered an increase in cardiac index ≥15% as a positive response rate. However, definite standards for FC administration and evaluation remain undefined. (Anesth Analg 2017;125:1562–45)

Critically ill patients often receive fluids to increase blood pressure or cardiac output (CO) by increasing the cardiac stroke volume (SV).[1,2] The fluid challenge (FC) is a diagnostic approach to hemodynamic management which aims at identifying the patients who respond to fluid administration with an increase in blood pressure or CO.[3] In this way, the FC can identify patients for whom use of inotropes or vasopressors is the appropriate strategy. Therapeutically, a positive FC suggests that fluid administration should be continued as long as the response to FC is positive.[4] The decision to stop fluid administration occurs when a negative response to FC occurs.

A patient is considered responsive to FC when hemodynamic improvement is observed after volemic expansion. While consensus exists on the use of FC to assess preload responsiveness,[1,2] the type of fluid, extent and rate of administration, and hemodynamic targets (either variable and thresholds) are not standardized in clinical practice. Cecconi et al,[1] after reviewing the key components of the FC and its clinical use in the intensive care unit (ICU), proposed the infusion of a standard volume of 500 mL (or 3 mL/kg) in 5 minutes, while guidelines for ICU management of patients with severe sepsis and septic shock propose 500–1000 mL of crystalloids or 300–500 mL of colloids in 30 minutes.[4] By selecting the extent of fluid responsiveness and hence the rate of responders, varying criteria for performing the FC and assessing the result FC may be interpreted by several studies.

Two large observational studies indicate that both the mode of administration and assessment of the FC in the current clinical practice vary considerably between countries and over time.[5,6] In particular, the 2015 FENICE trial, a recent prospective observational study performed in 251 ICUs located in 46 countries, found significant variability with respect to the amount and type of fluid and the rate of administration.[6] To address this issue, we systematically reviewed existing literature to evaluate whether the FC is

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Reprints will not be available from the author.

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Critical Care

RESEARCH Open Access

## What is the impact of the fluid challenge technique on diagnosis of fluid responsiveness? A systematic review and meta-analysis

Laura Taccone[1,2], Hollmann D. Ayo[1,2], Dimitris Anastasiadis[3,4], Davide Bassini[1,2], Vineeta Watson[1], Nish Anallurasan[1], Andrew Rhodes[1] and Maurizio Cecconi[1]

**Abstract**

**Background:** The fluid challenge is considered the gold standard for diagnosis of fluid responsiveness. The objective of this study was to describe the fluid challenge techniques reported in fluid responsiveness studies and to assess the difference in the proportion of 'responders' (PR) depending on the type of fluid, volume, duration of infusion and timing of assessment.

**Methods:** Searches of MEDLINE and Embase were performed for studies using the fluid challenge as a test of cardiac preload with a description of the technique, a reported definition of fluid responsiveness and PR. The primary outcome was the mean PR, depending on volume of fluid, type of fluid, rate of infusion and time of assessment.

**Results:** A total of 85 studies (3601 patients) were included in the analysis. The PR were 54.4% (95% CI 46.9–62.0) where >500 ml was administered, 57.2% (95% CI 52.3–61.9) where 500 ml was administered and 40.0% (95% CI 10.8–73.2) where <500 ml was administered ($p = 0.01$). The PR was not affected by type of fluid. The PR was similar among patients administered a fluid challenge for <15 minutes (50.2%, 95% CI 34.2–66.1) and for 15–30 minutes (57.3%, 95% CI 52.4–62.4, $p = 1$). Where the infusion time was 8–10 minutes, there was a lower PR of 49.9% (95% CI 45.6–54, $p = 0.01$). Response was assessed at the end of fluid challenge, between 1 and 10 minutes, and >10 minutes after the fluid challenge. The proportions of responders were 53.8%, 57.7% and 52.3%, respectively ($p = 0.47$).

**Conclusions:** The PR decreases with a long infusion time. A standard technique for fluid challenge is debatable.

**Keywords:** Fluid challenge, Fluid responsiveness, Fluid therapy, Fluid resuscitation

### Background

Intravenous fluid is one of the most commonly administered therapies for critically ill patients and is the cornerstone of hemodynamic management of patients in intensive care units (ICUs) [1]. The rationale for volemic expansion is to increase the cardiac output (CO) and oxygen delivery to ultimately improve tissue oxygenation. The gold standard for assessing fluid responsiveness is to guide fluid administration in critically ill patients is to perform a fluid challenge. This involves the infusion of a specific amount of intravenous fluid to assess ventricular preload reserve and subsequent systemic hemodynamic effects [2]. The volume of fluid infused must be sufficient to increase right ventricular diastolic volume and subsequently stroke volume (SV) as described by the Frank-Starling law [3]. Fluid responsiveness is conventionally defined as an increase of at least 10% to 15% in SV in response to a fluid challenge, which is a reflection of the limits of precision of the technology used [4, 5]. Patients who reach this threshold are considered 'fluid

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An abstract and alternative format of this work was presented at the annual congress of the European Society of Intensive Care Medicine in Milan in 2016.
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REVIEW

## Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data

Neil J Glassford[1,2], Glenn M Eastwood[1,3] and Rinaldo Bellomo[1,2]*

**Abstract**

Fluid bolus therapy (FBT) is a standard of care in the management of the septic, hypotensive, tachycardic and/or oliguric patient. However, contemporary evidence for FBT improving patient-centred outcomes is scant. Moreover, its physiological effects in contemporary ICU environments and populations are poorly understood. Using three electronic databases, we identified all studies describing FBT between January 2010 and December 2013. We found 31 studies describing 41 features. No randomised controlled trials compared FBT with alternative interventions, such as vasopressors. The median fluid bolus was 500 ml (range 100 to 1,000 ml) administered over 30 minutes (range 10 to 60 minutes) and the most commonly administered fluid was 0.9% sodium chloride solution. In 13 studies, a practitioner-mind physiological trigger initiated FBT. Although 17 studies describe the temporal course of physiological changes after FBT in 31 patient groups, only three studies describe the physiological changes at 60 minutes, and only one study beyond this point. No studies related the physiological changes after FBT with clinically relevant outcomes. There is a clear need for at least obtaining randomised controlled evidence for the physiological effects of FBT in patients with severe sepsis and septic shock beyond the period immediately after its administration.

Just as water retains no shape, so in warfare there are no constant conditions.
Sun Tzu | The Art of War |

### Introduction

All critically ill patients receive intravenous (IV) fluids, which are given to maintain physiological homeostasis, or as a vehicle for drug administration, or as direct therapeutic administration to correct perceived haemodynamic instability [1–4]. In those situations, where there is a perceived reduction in venous return and cardiac output secondary to vasodilatation and/or hypovolaemia, using IV fluid to increase intravascular volume is believed to effectively compensate for these changes in vascular tone by increasing stroke volume in accordance with the Frank-Starling principle [5–10].

Several mechanisms for delivering IV fluids, both diagnostically and therapeutically under such circumstances, have been described. These include 'Wells central venous pressure (CVP) guided fluid challenge technique [10–16],

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the timed and rapid infusion methods favoured by Shoemaker [7,8,14–16] and, more recently, techniques involving echocardiographic or ultrasonographic assessment of fluid responsiveness following low-volume IV infusion [17]. However, the current standard of care in the management of septic, hypotensive, tachycardic and/or oliguric patients is fluid bolus therapy (FBT), where IV fluid is rapidly administered in discrete boluses [18–21]. While the ideal fluid bolus would be a discrete volume of a specific fluid administered at a specified rate, accounting for individual patient features and with a defined aim (Figure 1) [11], there is no current agreement regarding exactly what defines a fluid bolus. Moreover, although strong overall consensus regarding the importance of FBT exists [18–20], there appears to be little randomised controlled information on the magnitude and duration of its physiological effects, or on the direct positive impact of FBT on patient outcome in sepsis as an independent intervention [22].

In contrast, an expanding body of evidence suggests that FBT may contribute to a positive fluid balance, which, in turn, is independently associated with a variety of adverse outcomes in the critically ill [23–26]. Recent



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*


## ABSTRACT

**BACKGROUND**

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to improve statistical power and explore heterogeneity of treatment effect of EGDT.

**METHODS**

We harmonized entry criteria, intervention protocols, outcomes, resource-use measures, and data collection across the trials and specified all analyses before unblinding. After completion of the trials, we pooled data, excluding the protocol-based standard-therapy group from the ProCESS trial, and resolved residual differences. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs. We tested for treatment-by-subgroup interactions for 16 patient characteristics and 6 care-delivery characteristics.

**RESULTS**

We studied 3723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% confidence interval, 0.82 to 1.14; P=0.68). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P=0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P=0.01) than was usual care; other outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

**CONCLUSIONS**

In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. (Funded by the National Institute of General Medical Sciences and others; PRISM ClinicalTrials.gov number, NCT02030158.)


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**Table 1. Patient and Care-Delivery Characteristics at Baseline.***

| Care-delivery characteristics | | |
|---|---|---|
| Time from ED presentation to inclusion criteria met — min | | |
| Median | 85 | 81 |
| IQR | 40–150 | 36–145 |
| Time from ED presentation to randomization — min | | |
| Median | 162 | 159 |
| IQR | 119–223 | 115–221 |
| Receiving antimicrobial agents at randomization — no./total no. (%) | 1726/1856 (93.0) | 1742/1880 (92.7) |
| Time from ED presentation to first IV antimicrobial agents — min** | | |
| Median | 75 | 72 |
| IQR | 42–120 | 42–119 |
| IV fluids administered before hospital presentation until randomization — no./total no. (%) | 1801/1846 (97.6) | 1818/1871 (97.2) |
| Volume administered — ml | | |
| Median | 2000 | 2000 |
| IQR | 1250–3000 | 1200–3000 |
| Volume administered per kilogram of body weight — ml | | |
| Median | 27.5 | 27.7 |
| IQR | 16.5–42.3 | 16.2–41.7 |

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| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | Small | Moderate | Large | | **Varies** | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | Small | Trivial | | **Varies** | Don't know |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **ACCEPTABILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

# Summary of judgements: Conditional recommendation for the intervention (30ml/kg)

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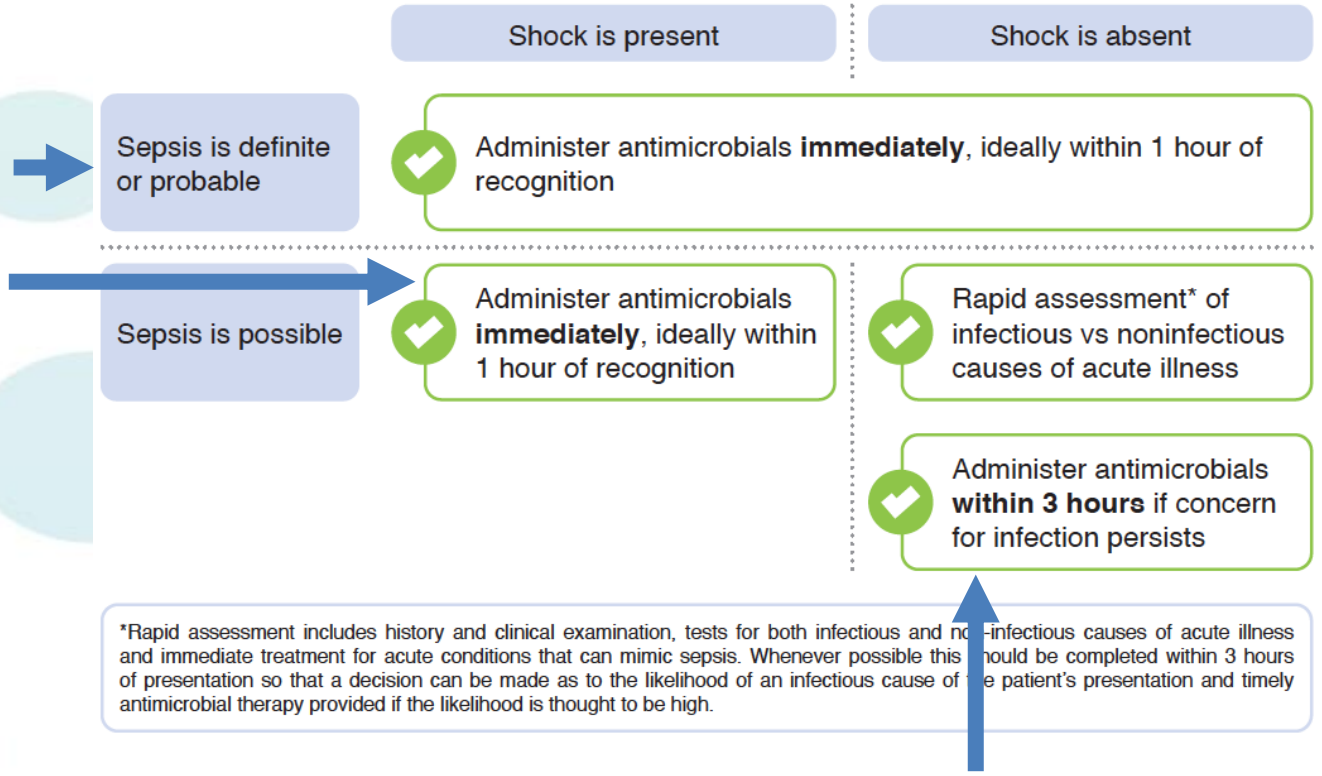
# Initiation of antimicrobials

For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hour of recognition. (Strong recommendation, low QOE for shock, very low for sepsis without shock)




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, low QOE)

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# Liberal or restrictive fluid strategies

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In patients with sepsis and septic shock, should we use a restrictive fluid management in the first 24 hours of resuscitation? | **There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hr 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 |

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# Evidence profile - Liberal or restrictive fluid strategy

| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | restrictive fluid | non-restrictive fluid | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | serious [a] | serious [b] | none | 69/236 (29.2%) | 71/235 (30.2%) | RR 0.98 (0.76 to 1.28) | 6 fewer per 1,000 (from 73 fewer to 85 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Renal replacement therapy** | | | | | | | | | | | | |
| 4 | randomised trials | not serious [c] | not serious | serious [a] | serious [b] | none | 92/229 (40.2%) | 93/235 (39.6%) | RR 1.00 (0.91 to 1.10) | 0 fewer per 1,000 (from 36 fewer to 40 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **New onset organ dysfunction - cardiovascular (vasopressor for shock)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious [c] | not serious | serious [a] | very serious [b] | none | 47/55 (85.5%) | 43/54 (79.6%) | RR 1.07 (0.90 to 1.28) | 56 more per 1,000 (from 80 fewer to 223 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **New onset organ dysfunction - respiratory (new mechanical ventilation)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious [c] | not serious | serious [a] | very serious [b] | none | 15/53 (28.3%) | 17/52 (32.7%) | RR 0.87 (0.49 to 1.55) | 43 fewer per 1,000 (from 167 fewer to 180 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **New onset organ dysfunction - new hemodialysis** | | | | | | | | | | | | |
| 1 | randomised trials | not serious [c] | not serious | serious [a] | very serious [b] | none | 1/48 (2.1%) | 2/53 (3.8%) | RR 0.55 (0.05 to 5.90) | 17 fewer per 1,000 (from 36 fewer to 185 | ⊕◯◯◯ VERY LOW | CRITICAL |

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# High flow nasal oxygen

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In adults with sepsis-induced hypoxemic respiratory failure, should we use high flow nasal oxygen compared to non-invasive ventilation? | **For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over noninvasive ventilation.** | Weak recommendation, low quality of evidence | New recommendation |

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# Evidence profile – HFNO

| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | HFNO therapy | NIV | Relative (95% CI) | Absolute (95% CI) | | |
| **ICU Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 12/106 (11.3%) | 27/110 (24.5%) | RR 0.46 (0.25 to 0.86) | 133 fewer per 1,000 (from 184 fewer to 34 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **Mortality at Day 90** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 13/106 (12.3%) | 31/110 (28.2%) | RR 0.44 (0.24 to 0.79) | 158 fewer per 1,000 (from 214 fewer to 59 fewer) | ⊕⊕◯◯ LOW | CRITICAL |
| **Need for Intubation** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a,b] | none | 40/106 (37.7%) | 55/110 (50.0%) | RR 0.75 (0.55 to 1.03) | 125 fewer per 1,000 (from 225 fewer to 15 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Ventilator Free Days at Day 28** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 106 | 110 | - | MD 5 higher (2.29 higher to 7.71 higher) | ⊕⊕◯◯ LOW | IMPORTANT |

Evidence profile based on single RCT comparing HFNO to NIV (FLORALI trial)



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# Vitamin C

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In adults with sepsis or septic shock, should we use intravenous vitamin C? | **For adults with sepsis or septic shock we suggest against using IV vitamin C.** | Weak recommendation, low quality of evidence | New recommendation |



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# Evidence profile* – Vitamin C

| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | intravenous vitamin C | not | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 7 | randomised trials | not serious | serious [a] | not serious | serious [b] | none | 69/219 (31.5%) | 88/207 (42.5%) | RR 0.79 (0.57 to 1.10) | 89 fewer per 1,000 (from 183 fewer to 43 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Organ failure (follow up: 96 hours)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious [b] | none | 83 | 84 | - | SMD 0.1 SD lower (1.23 lower to 1.03 higher) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Vasopressor use (follow up: 168 hours)** | | | | | | | | | | | | |
| 1 [c] | randomised trials | not serious | not serious | not serious | very serious [d] | none | 16/72 (22.2%) | 6/59 (10.2%) | RR 2.19 (0.91 to 5.23) | 121 more per 1,000 (from 9 fewer to 430 more) | ⊕⊕◯◯ LOW | IMPORTANT |

*The VICTAS trial was published after the conclusion of the literature review period



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# Sepsis education for patients/families

| PICO Question | 2021 Recommendation | Recommendation Strength and Quality | Change from 2016 |
|---|---|---|---|
| In adult sepsis survivors and family members, does providing focused sepsis education (eg. booklets, apps, websites) during the hospitalization and at hospital discharge, compared to no such education, increase satisfaction, knowledge, improve psychological outcomes, and reduce ICU and hospital readmission? | **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.** | No recommendation | New |



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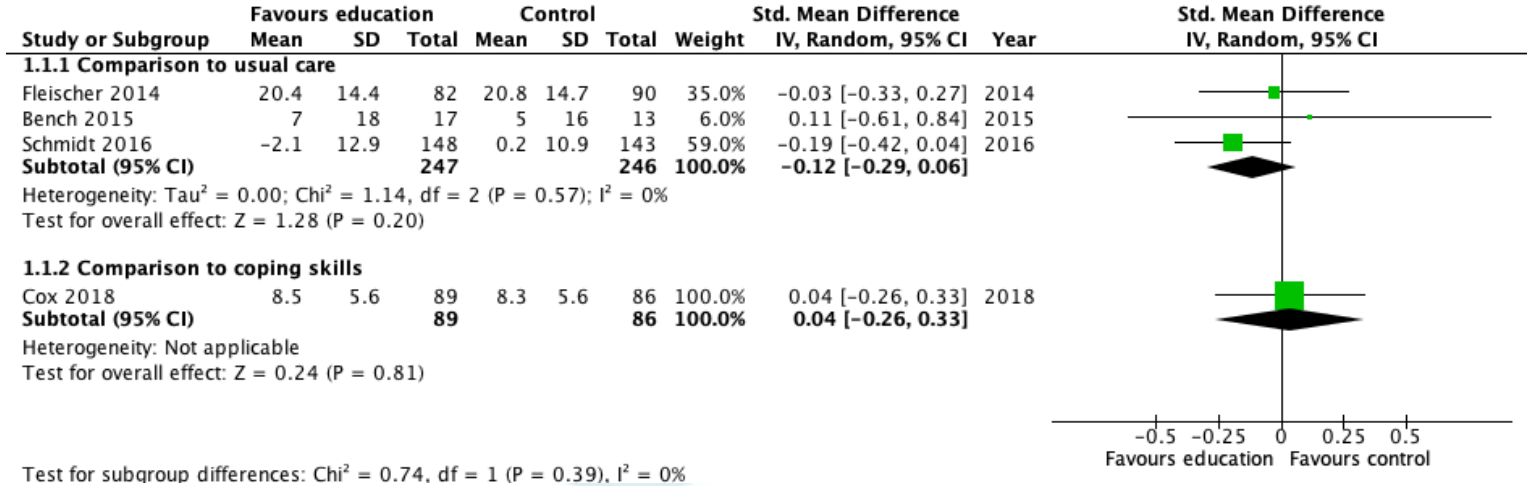
# Evidence: Sepsis education for patients/families

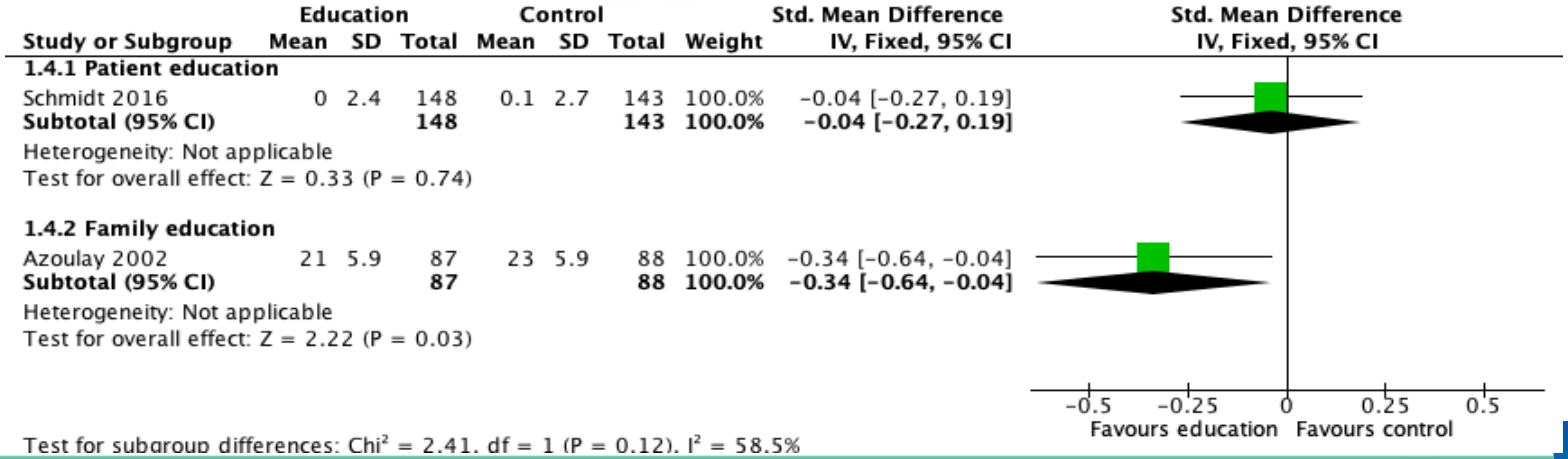
Outcome:
Patient anxiety



| Study or Subgroup | Favours education Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| **1.1.1 Comparison to usual care** | | | | | | | | | |
| Fleischer 2014 | 20.4 | 14.4 | 82 | 20.8 | 14.7 | 90 | 35.0% | -0.03 [-0.33, 0.27] | 2014 |
| Bench 2015 | 7 | 18 | 17 | 5 | 16 | 13 | 6.0% | 0.11 [-0.61, 0.84] | 2015 |
| Schmidt 2016 | -2.1 | 12.9 | 148 | 0.2 | 10.9 | 143 | 59.0% | -0.19 [-0.42, 0.04] | 2016 |
| **Subtotal (95% CI)** | | | **247** | | | **246** | **100.0%** | **-0.12 [-0.29, 0.06]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.57); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | | | | | | |
| **1.1.2 Comparison to coping skills** | | | | | | | | | |
| Cox 2018 | 8.5 | 5.6 | 89 | 8.3 | 5.6 | 86 | 100.0% | 0.04 [-0.26, 0.33] | 2018 |
| **Subtotal (95% CI)** | | | **89** | | | **86** | **100.0%** | **0.04 [-0.26, 0.33]** | |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | | | | |
| Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0% | | | | | | | | | |



Outcome:
Satisfaction with care



| Study or Subgroup | Education Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.4.1 Patient education** | | | | | | | | |
| Schmidt 2016 | 0 | 2.4 | 148 | 0.1 | 2.7 | 143 | 100.0% | -0.04 [-0.27, 0.19] |
| **Subtotal (95% CI)** | | | **148** | | | **143** | **100.0%** | **-0.04 [-0.27, 0.19]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | | | |
| **1.4.2 Family education** | | | | | | | | |
| Azoulay 2002 | 21 | 5.9 | 87 | 23 | 5.9 | 88 | 100.0% | -0.34 [-0.64, -0.04] |
| **Subtotal (95% CI)** | | | **87** | | | **88** | **100.0%** | **-0.34 [-0.64, -0.04]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.22 (P = 0.03) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.41, df = 1 (P = 0.12), I² = 58.5% | | | | | | | | |





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# 93 total recommendations

- Several new recommendations regarding
  - Capillary refill time
  - Empiric MRSA coverage
  - Empiric fungal coverage
  - Peripheral vasopressor use
  - Levosimendan
  - HFNC and NIV
  - Use of ECMO
  - Post-ICU follow up



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# Thank you!
# Time for discussion...



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