

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Surviving Sepsis Campaign

COI Disclosures

- Evans – Nothing to disclose

Thank You

- Guidelines panelists
- Group Heads
- Methodologists
- SCCM and ESICM
- Participating societies
- Reviewers
- Dr. Phil Dellinger
- Ms. Deb McBride

Timeline of the SSC Guidelines

- First edition in 2004
- Previous Revisions in 2008 and 2012
- Current revision started in 2014
- Jointly sponsored by ESICM and SCCM

Structure of the Guidelines

- **SSC Guidelines Committee Oversight Group**
 - Andrew Rhodes, Laura Evans, Mitchell Levy
- **SSC Guidelines Committee Group Heads**
 - Massimo Antonelli (Hemodynamics), Ricard Ferrer (Adjunctive), Anand Kumar (Infection), Jonathan E. Sevransky (Ventilation), Charles L. Sprung (Metabolic)
- **GRADE Methodology Group**
 - Waleed Alhazzani (chair), Mark E. Nunnally, Bram Rochwerg
- **Conflict of Interest Chair**
 - Gordon Rubenfeld

SSC Guidelines Panel Members

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- Laura E. Evans, MD, MSc, FCCM
- Waleed Alhazzani, MD, MSc, FRCPC
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- Khalid A. Shukri, MD
- Steven Q. Simpson, MD
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- B. Taylor Thompson, MD
- Sean R. Townsend, MD
- Thomas Van der Poll, MD
- Jean-Louis Vincent, MD, PhD, FCCM
- W. Joost Wiersinga, MD, PhD
- Janice L. Zimmerman, MD, MACP, MCCM
- R. Phillip Dellinger, MD, MCCM

Management of Potential Conflict of Interest

- No industry input
- Panelists did not receive honoraria
- Personal disclosure of potential COI upon joining guidelines panel and annually
- Management of potential COI
 - Limited voting on topics pertinent to COI
 - Group reassignment

Sepsis-3 Definitions

- ***Sepsis***: Life-threatening organ dysfunction caused by dysregulated host response to infection
- ***Septic Shock***: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality

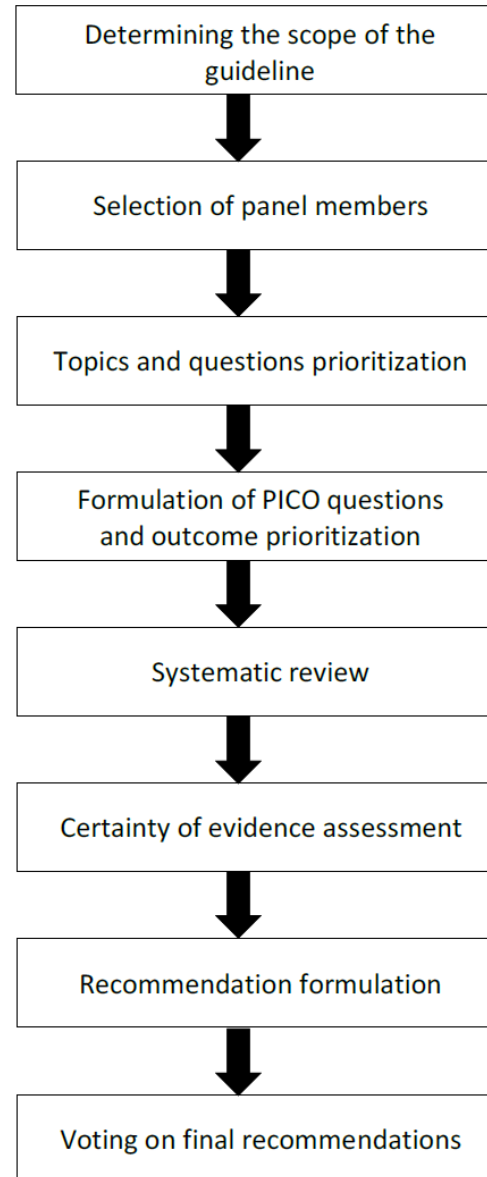
JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

SSC Guidelines and Sepsis-3 Definitions

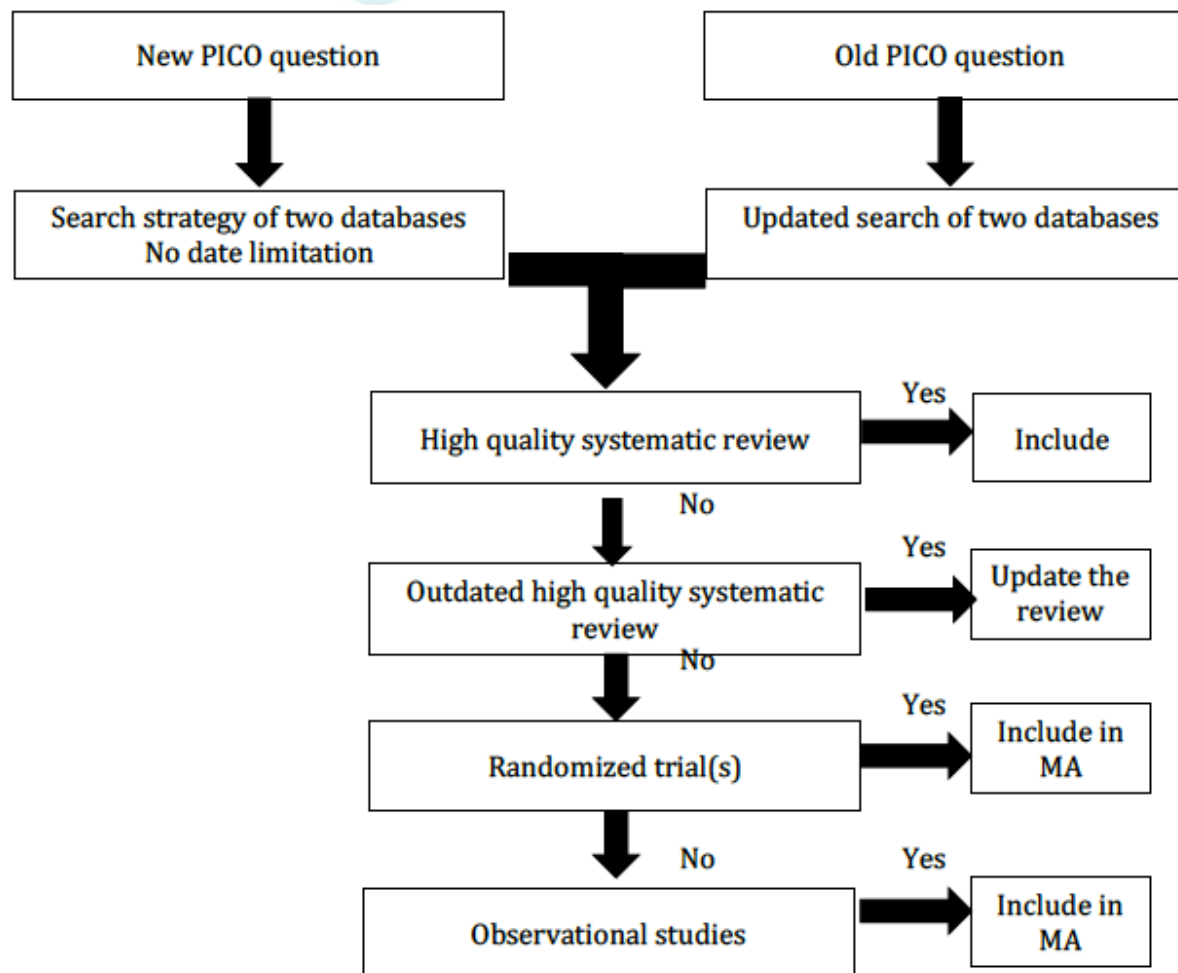
- ***“Sepsis”*** in place of ***“Severe Sepsis”***
- Sepsis-3 clinical criteria (i.e. qSOFA) were not used in studies that informed the recommendations in this revision
 - Could not comment on use of Sepsis-3 clinical criteria

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

SSC Guidelines Process



Study Selection



SSC Guideline Process

- PICO Question Review and Development
- Literature searches
 - Minimum of 2 major databases
 - Assistance from professional librarians
- Generation of evidence profiles
- Grading of recommendations
 - GRADE
- Voting
 - 80% agreement required
- Reformulation and re-voting as needed

GRADE: Quality of Evidence

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias
- Other criteria

Determination of Quality of Evidence

Underlying methodology

1. High: RCTs
2. Moderate: Downgraded RCTs or upgraded observational studies
3. Low: Well-done observational studies
4. Very Low: Downgraded controlled studies or expert opinion or other evidence

Determination of Quality of Evidence

Factors that may decrease the strength of evidence

1. Methodologic features of RCTs suggesting high likelihood of bias
2. Inconsistency of results, including problems with subgroup analyses
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Determination of Quality of Evidence

Main factors that may increase the strength of evidence

1. Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradient

Factors determining strong versus weak recommendations

What Should Be Considered	Recommended Process
High or moderate quality of evidence	The higher the quality of evidence, the more likely a strong recommendation
Certainty about the balance of benefits vs. harms and burdens	<ul style="list-style-type: none">- A larger difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation.- The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.
Certainty in, or similar, values	The more certainty or similarity in values and preferences, the more likely a strong recommendation.
Resource implications	The lower the cost of an intervention compared to the alternative and other costs related to the decision (i.e., fewer resources consumed), the more likely a strong recommendation.

Best Practice Statements

- Strong but ungraded statements
- Use defined criteria

Criteria for Best Practice Statements

Is the statement clear and actionable?

Is the message necessary?

Is the net benefit (or harm) unequivocal?

Is the evidence difficult to collect and summarize?

Is the rationale explicit?

Is the statement better if formally GRADEd?

Prose GRADE descriptions

	2016 Descriptor	2012 Descriptor
Strength	Strong Weak	1 2
Quality	High Moderate Low Very Low	A B C D
Ungraded Strong Recommendation	Best Practice Statement	Ungraded Strong Recommendation

Implications of the strength of a recommendation

	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.

Recommendations

- 93 Recommendations
 - 32 **Strong** recommendations: “***We recommend***”
 - 39 **Weak** recommendations: “***We suggest***”
 - 18 Best Practice Statements
 - No recommendation provided for 4 PICO questions

COI Disclosures

- Rhodes– Nothing to disclose

CONFERENCE REPORTS AND EXPERT PANEL



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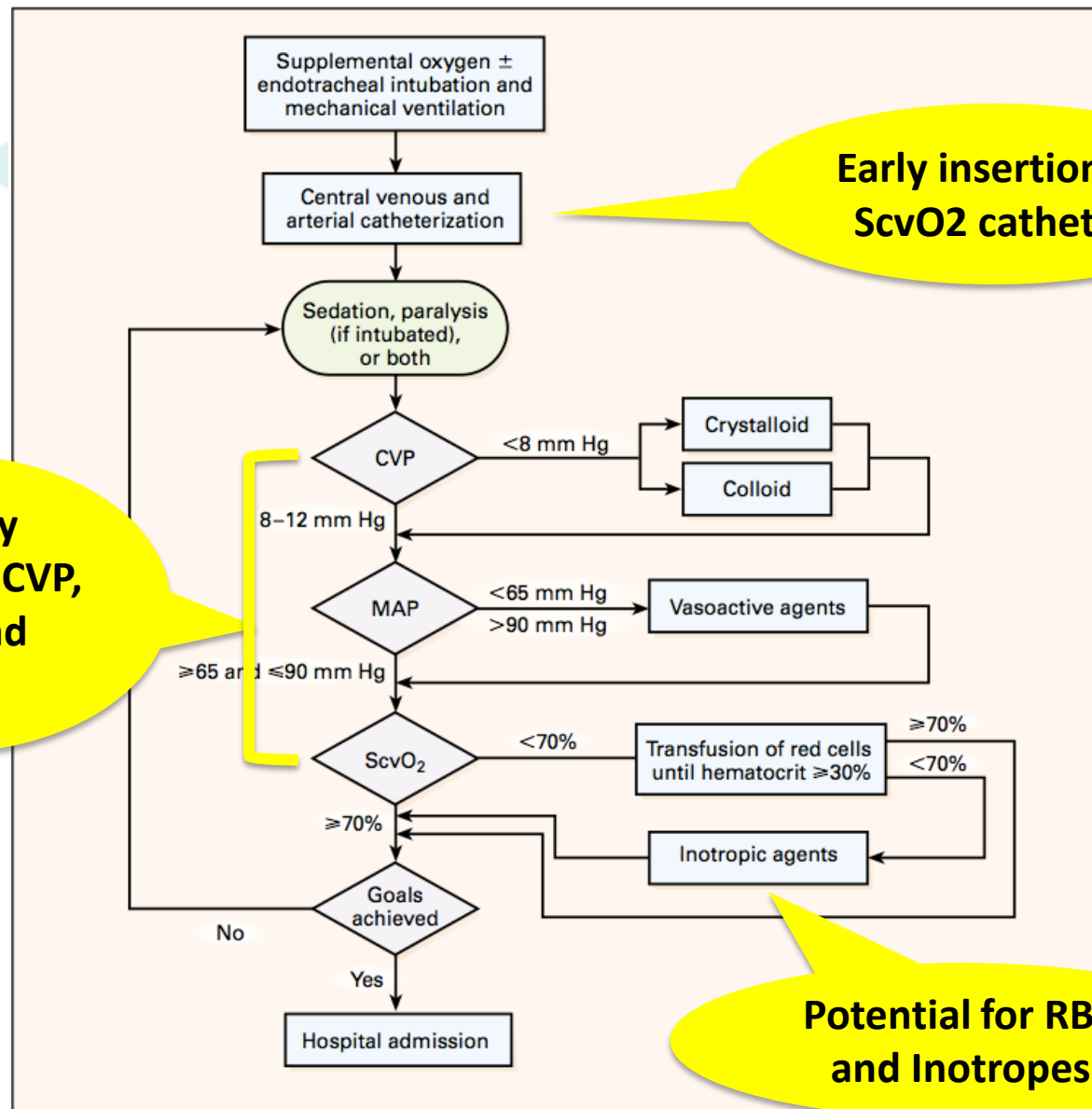
Andrew Rhodes^{1*}, Laura E. Evans², Waleed Alhazzani³, Mitchell M. Levy⁴, Massimo Antonelli⁵, Ricard Ferrer⁶, Anand Kumar⁷, Jonathan E. Sevransky⁸, Charles L. Sprung⁹, Mark E. Nunnally², Bram Rochwerg³, Gordon D. Rubenfeld¹⁰, Derek C. Angus¹¹, Djillali Annane¹², Richard J. Beale¹³, Geoffrey J. Bellinghan¹⁴, Gordon R. Bernard¹⁵, Jean-Daniel Chiche¹⁶, Craig Coopersmith⁸, Daniel P. De Backer¹⁷, Craig J. French¹⁸, Seitaro Fujishima¹⁹, Herwig Gerlach²⁰, Jorge Luis Hidalgo²¹, Steven M. Hollenberg²², Alan E. Jones²³, Dilip R. Karnad²⁴, Ruth M. Kleinpell²⁵, Younsuk Koh²⁶, Thiago Costa Lisboa²⁷, Flavia R. Machado²⁸, John J. Marini²⁹, John C. Marshall³⁰, John E. Mazuski³¹, Lauralyn A. McIntyre³², Anthony S. McLean³³, Sangeeta Mehta³⁴, Rui P. Moreno³⁵, John Myburgh³⁶, Paolo Navalesi³⁷, Osamu Nishida³⁸, Tiffany M. Osborn³¹, Anders Perner³⁹, Colleen M. Plunkett²⁵, Marco Ranieri⁴⁰, Christa A. Schorr²², Maureen A. Seckel⁴¹, Christopher W. Seymour⁴², Lisa Shieh⁴³, Khalid A. Shukri⁴⁴, Steven Q. Simpson⁴⁵, Mervyn Singer⁴⁶, B. Taylor Thompson⁴⁷, Sean R. Townsend⁴⁸, Thomas Van der Poll⁴⁹, Jean-Louis Vincent⁵⁰, W. Joost Wiersinga⁴⁹, Janice L. Zimmerman⁵¹ and R. Phillip Dellinger²²

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2012 Recommendation for Initial Resuscitation.

We recommend the **protocolized**, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the **goals of initial resuscitation should include all** of the following as a part of a treatment protocol:

- a) CVP 8–12 mm Hg
- b) MAP \geq 65 mm Hg
- c) Urine output \geq 0.5 mL/kg/hr
- d) Scvo2 \geq 70%.



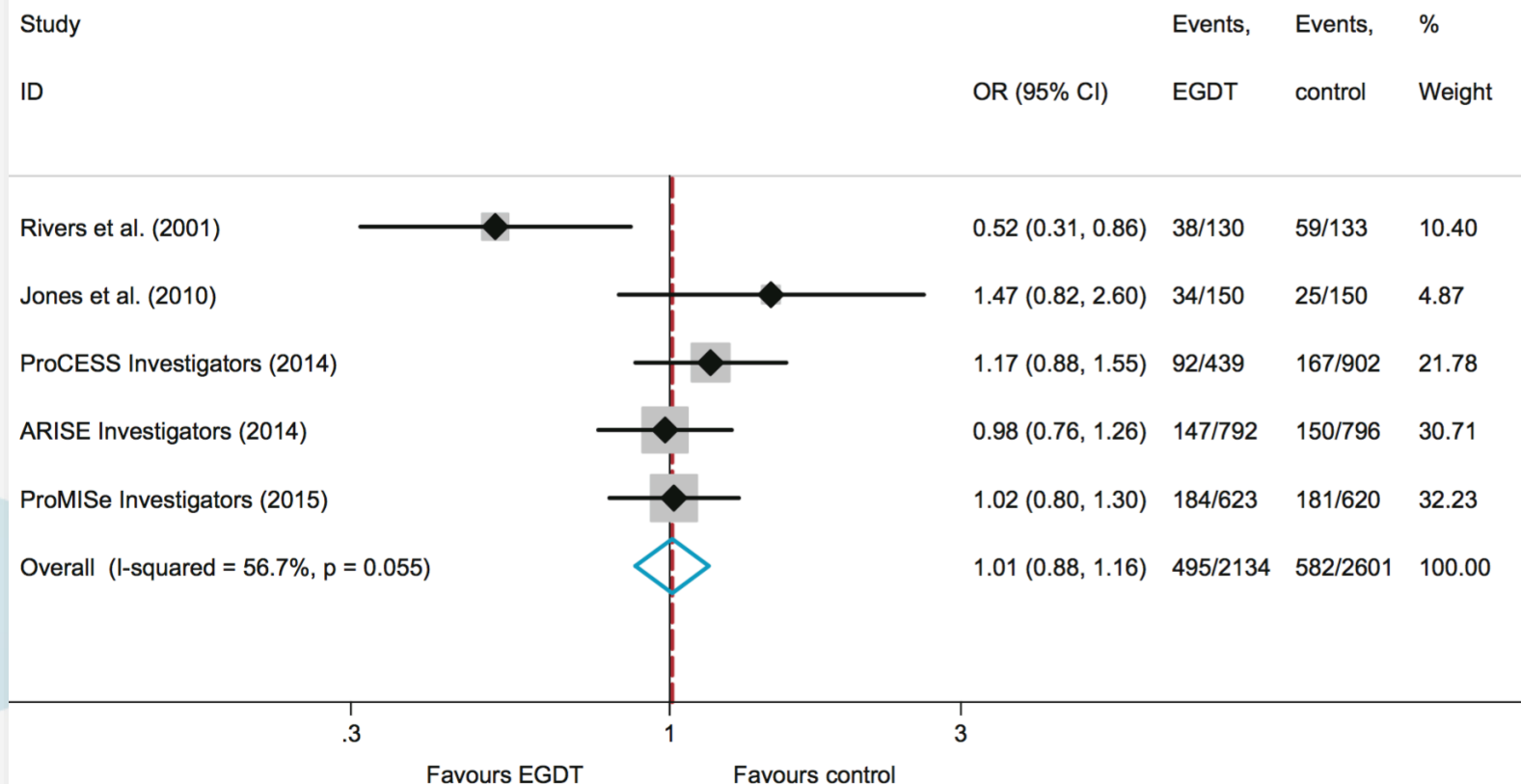
Early insertion of ScvO₂ catheter

Therapy titrated to CVP, MAP and ScvO₂

Potential for RBC and Inotropes

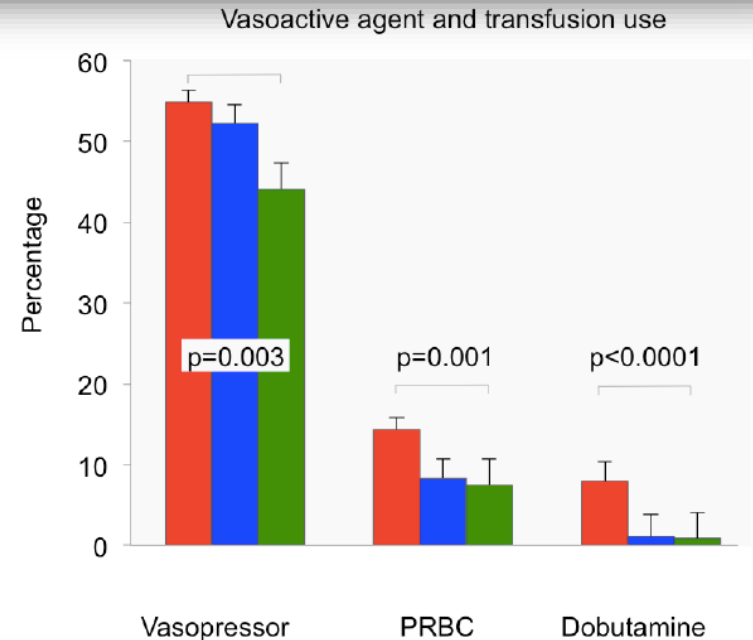
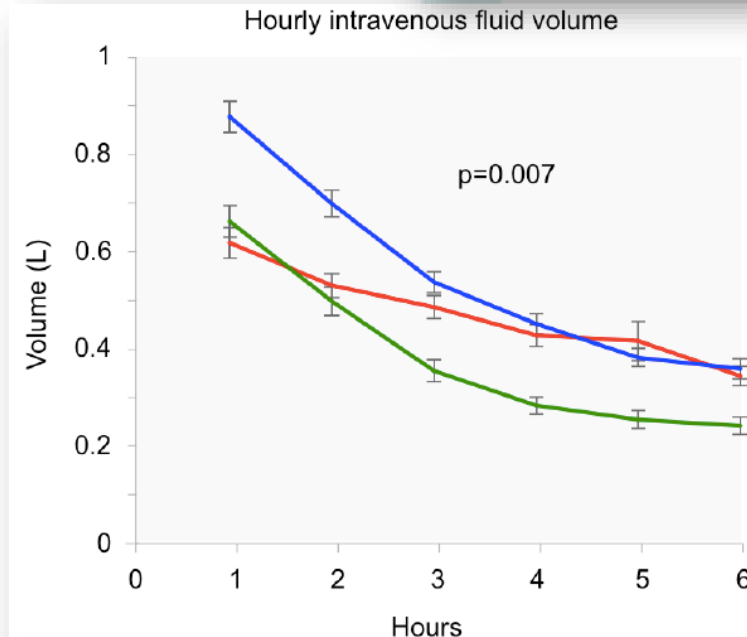
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMiSe Investigators

A Primary mortality outcome of each study



A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*



Protocol-based EGDT

Protocol-based Standard Therapy

Usual care

Intravenous Fluids

EGDT 2.8 L

Usual Care 2.3 L

Intravenous Antibiotics

EGDT 97.5%

Usual Care 96.9%

Caveats / Limitations of ProCESS, ARISE & Promise

- **The overall management of sepsis has changed...**
 - In all three studies patients had early antibiotics, > 30ml/kg of intravenous fluid prior to randomization.
- **We need therefore to be very careful about over interpreting the results in areas where this paradigm is not valid.**

The River's work was useful....

- As it provided us a construct on how to understand resuscitation:
 - Start early- (give antibiotics)
 - Correct hypovolaemia
 - Restore perfusion pressure
 - And in some cases a little more may be required..!
- These concepts are as important today as they ever were.

Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.

Best Practice Statement

Source Control

- **We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.**

(Best Practice Statement).

Antibiotics

- **We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

- **We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

Initial Resuscitation

- **We recommend that in the 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)

- **We recommend that following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.**

(Best Practice Statement)

Fluid Therapy

- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

(weak recommendation, low quality of evidence).

High versus Low Blood-Pressure Target in Patients with Septic Shock

We recommend an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors.

(Strong recommendation; moderate quality of evidence)

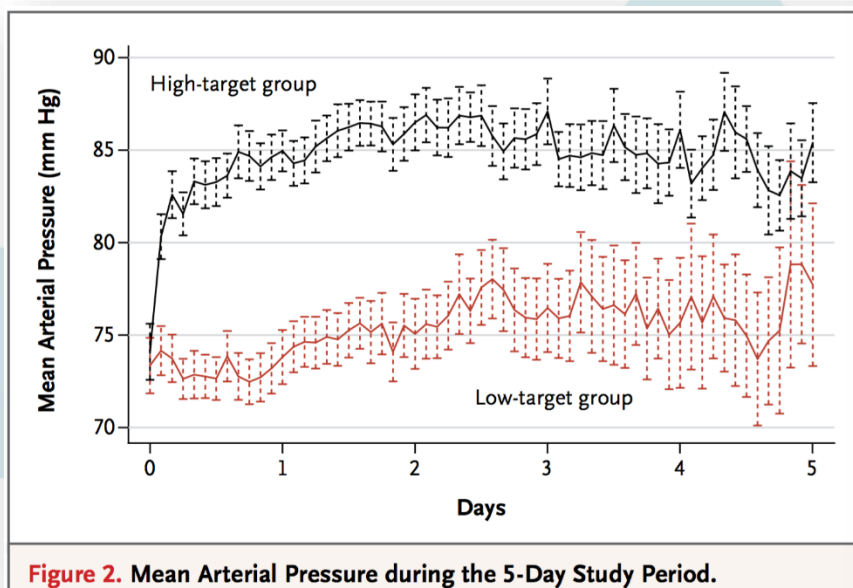


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

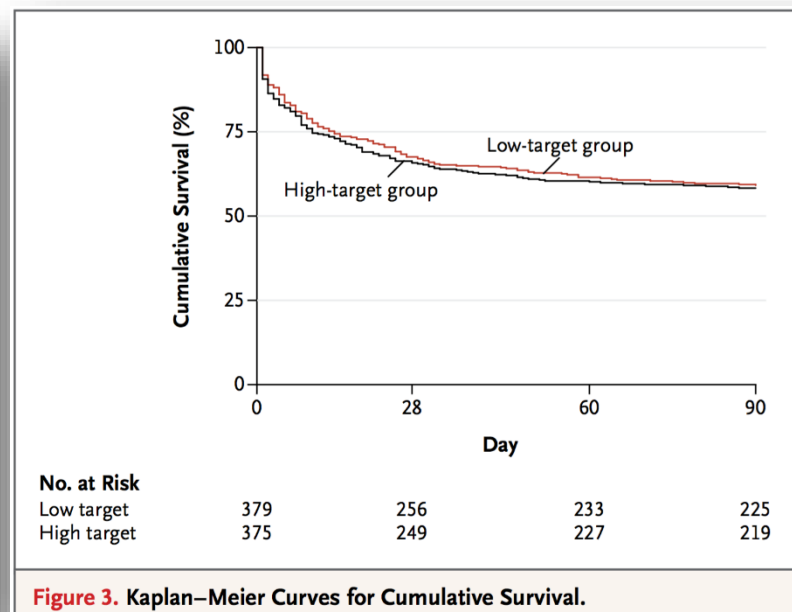


Figure 3. Kaplan-Meier Curves for Cumulative Survival.

Vasoactive agents

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

If shock is not resolving quickly.....

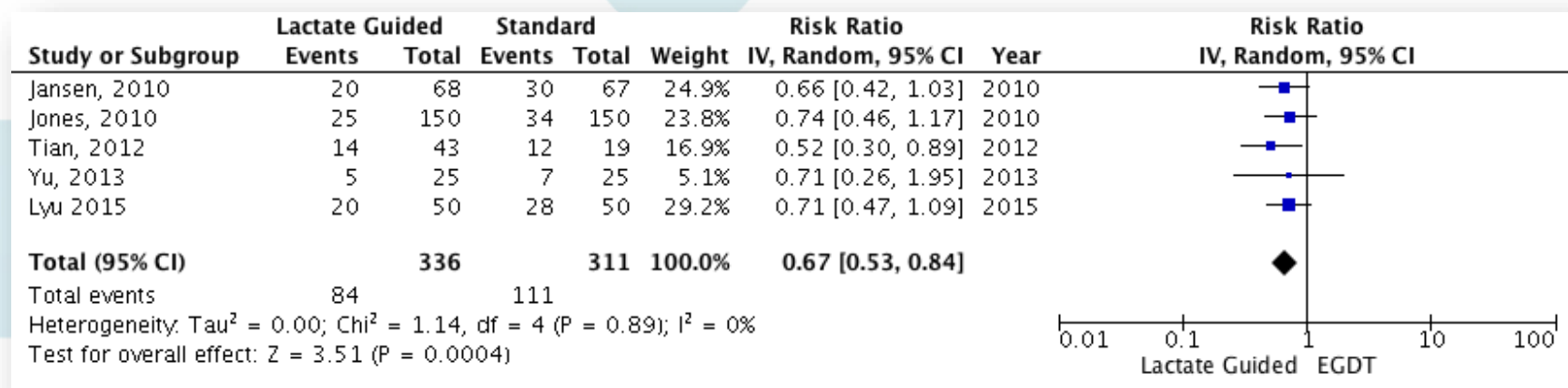
- **We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis.**
(Best Practice Statement)
- **We suggest that dynamic over static variables be used to predict fluid responsiveness, where available.**

(Weak recommendation; low quality of evidence)

Lactate can help guide resuscitation

- We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

(Weak recommendation; low quality of evidence)



Summary

- **Start resuscitation early with source control, intravenous fluids and antibiotics.**
- **Frequent assessment of the patients' volume status is crucial throughout the resuscitation period.**
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

- 1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients. (BPS)**

Sepsis Performance Improvement

- Performance improvement efforts for sepsis are associated with improved patient outcomes
- A recent meta-analysis of 50 observational studies:
 - Performance improvement programs associated with a significant increase in compliance with the SSC bundles and a reduction in mortality (OR 0.66; 95% CI 0.61-0.72).
- Mandated public reporting:
 - NYS, CMS, UK

Diagnosis

- **1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials. (BPS)**
 - **Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).**

Antibiotics

- **We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.**
 - **(Weak recommendation; low quality of evidence)**

Antibiotics

- **We suggest that combination therapy not be routinely used for on-going treatment of most other serious infections, including bacteremia and sepsis without shock.**
 - (Weak recommendation; low quality of evidence).
- **We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia.**
 - (Strong recommendation; moderate quality of evidence).

Antimicrobial Therapy

Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
 - (BPS)
- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
 - (Weak recommendation; low quality of evidence)
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
 - (BPS)
- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
 - (Weak recommendation; low quality of evidence)

CORTICOSTEROIDS

- 1. We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day. (Weak recommendation; low quality of evidence)**

Mechanical Ventilation

- **We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS.**
 - Weak recommendation; moderate quality of evidence
- **We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a $\text{PaO}_2/\text{FIO}_2$ ratio <150 .**
 - (Strong recommendation; moderate quality of evidence)

Mechanical Ventilation

- **We recommend against the use of HFOV in adult patients with sepsis-induced ARDS.**
 - (Strong recommendation; moderate quality of evidence)
- **We recommend against the use of beta-2 agonists for the treatment of patients with sepsis- induced ARDS without bronchospasm.**
 - (Strong recommendation; moderate quality of evidence)

Mechanical Ventilation

- **We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS.**
 - (Weak recommendation; low quality of evidence)

GLUCOSE CONTROL

- 1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤ 180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL. (Strong recommendation; high quality of evidence)**
- 2. We recommend that blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter in patients receiving insulin infusions. (BPS)**

GLUCOSE CONTROL

- 3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values. (BPS)**
- 4. We suggest the use of arterial blood rather than capillary blood for point of care testing using glucose meters if patients have arterial catheters. (Weak recommendation; low quality of evidence)**

Renal Replacement Therapy

- **We suggest against the use of renal replacement therapy in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.**
 - (Weak recommendation; low quality of evidence)

Nutrition

- **We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally. (Strong recommendation; moderate quality of evidence)**

Nutrition

- **We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock in whom early enteral feeding is not feasible. (Strong recommendation; moderate quality of evidence).**

Nutrition

- **We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally. (Weak recommendation; low quality of evidence)**
- **We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance. (Weak recommendation; moderate quality of evidence)**

Nutrition

- **We suggest against routinely monitoring gastric residual volumes in critically ill patients with sepsis or septic shock. (Weak recommendation; low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be high risk for aspiration. (Weak recommendation; very low quality of evidence)**

Nutrition

- **We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance. (Weak recommendation; low quality of evidence)**

Setting Goals of Care

- We recommend that goals of care and prognosis be discussed with patients and families. (BPS)
- We recommend that the goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate. (Strong recommendation; moderate quality of evidence)
- We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission. (Weak recommendation; low quality of evidence)

Surviving Sepsis Campaign



Thank You!