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The Ever Changing World of Sepsis Management

Laura Evans MD MSc

Medical Director of Critical Care

Bellevue Hospital

COI Disclosures

- No financial interests to disclose

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Learning Objectives

- Review the evolution of the SSC Guidelines
- Discuss new/changed recommendations of revised SSC Guidelines
- Describe areas of ongoing controversy in sepsis
  - Focus on resuscitation and antibiotic therapy

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Timeline of the SSC Guidelines

- First edition in 2004
- Previous Revisions in 2008 and 2012
- Jointly sponsored by ESICM and SCCM
- Jointly published in *Critical Care Medicine* and *Intensive Care Medicine*
- SSC Bundles are updated by QI group within SSC

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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

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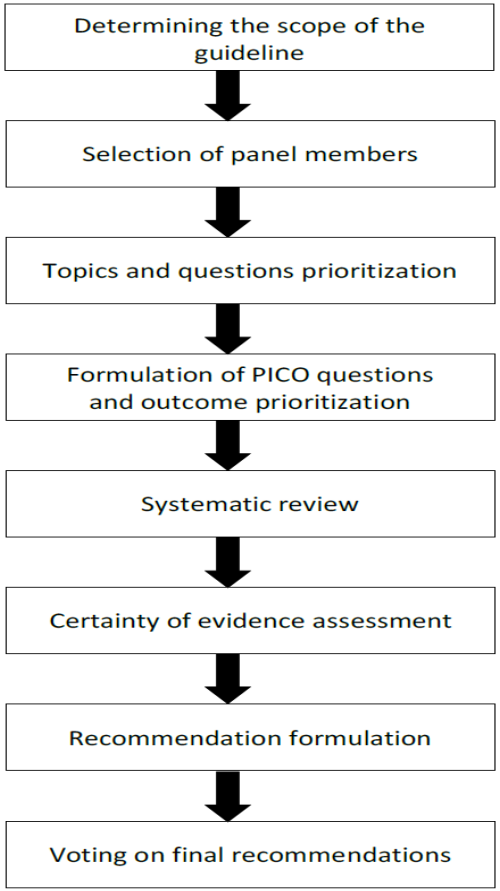
SSC Guidelines Process



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SSC Guidelines 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

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GRADE: Quality of Evidence

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

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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

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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

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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	- 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?

Guyatt GH, Schünemann HJ, Djulbegovic B, et al: *Clin Epidemiol* 2015; 68:597–600

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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

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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

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First Challenge: 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

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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

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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 ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%

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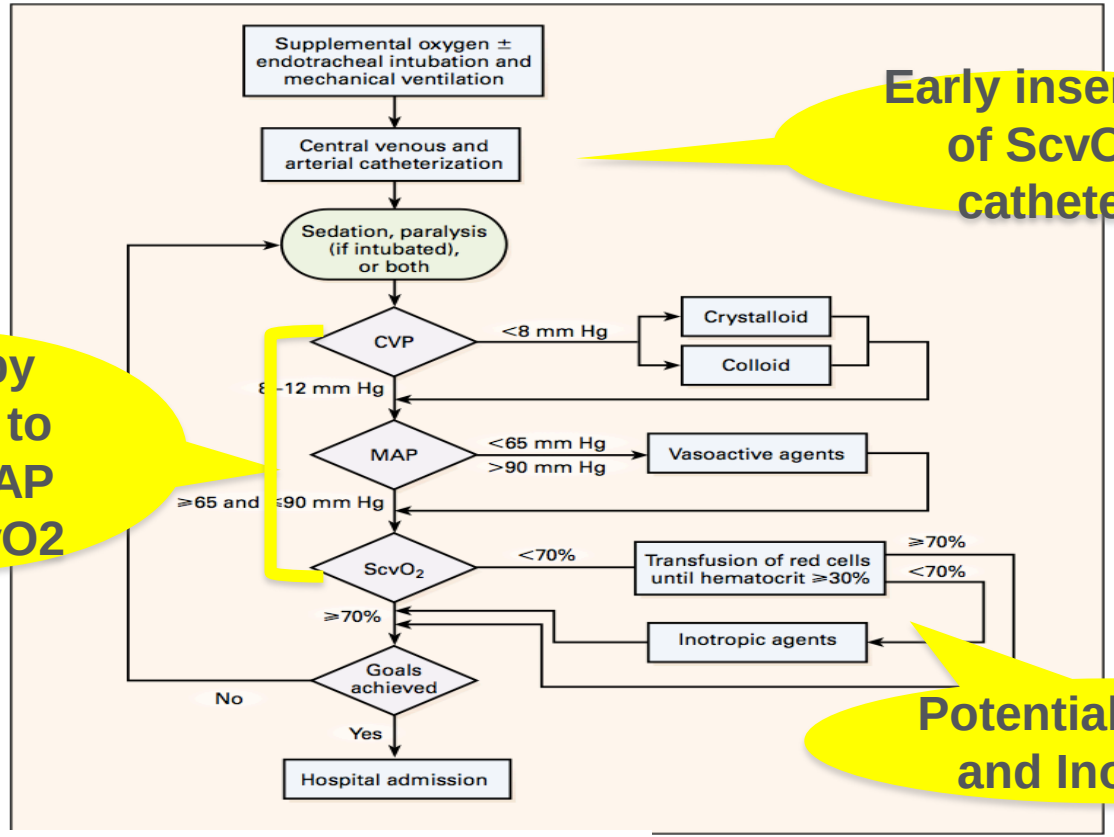
Rivers Protocol



Early insertion of ScvO2 catheter

Therapy titrated to CVP, MAP and ScvO2

Potential for RBC and Inotropes

N Engl J Med, Vol. 345, No. 19 · November 8, 2001

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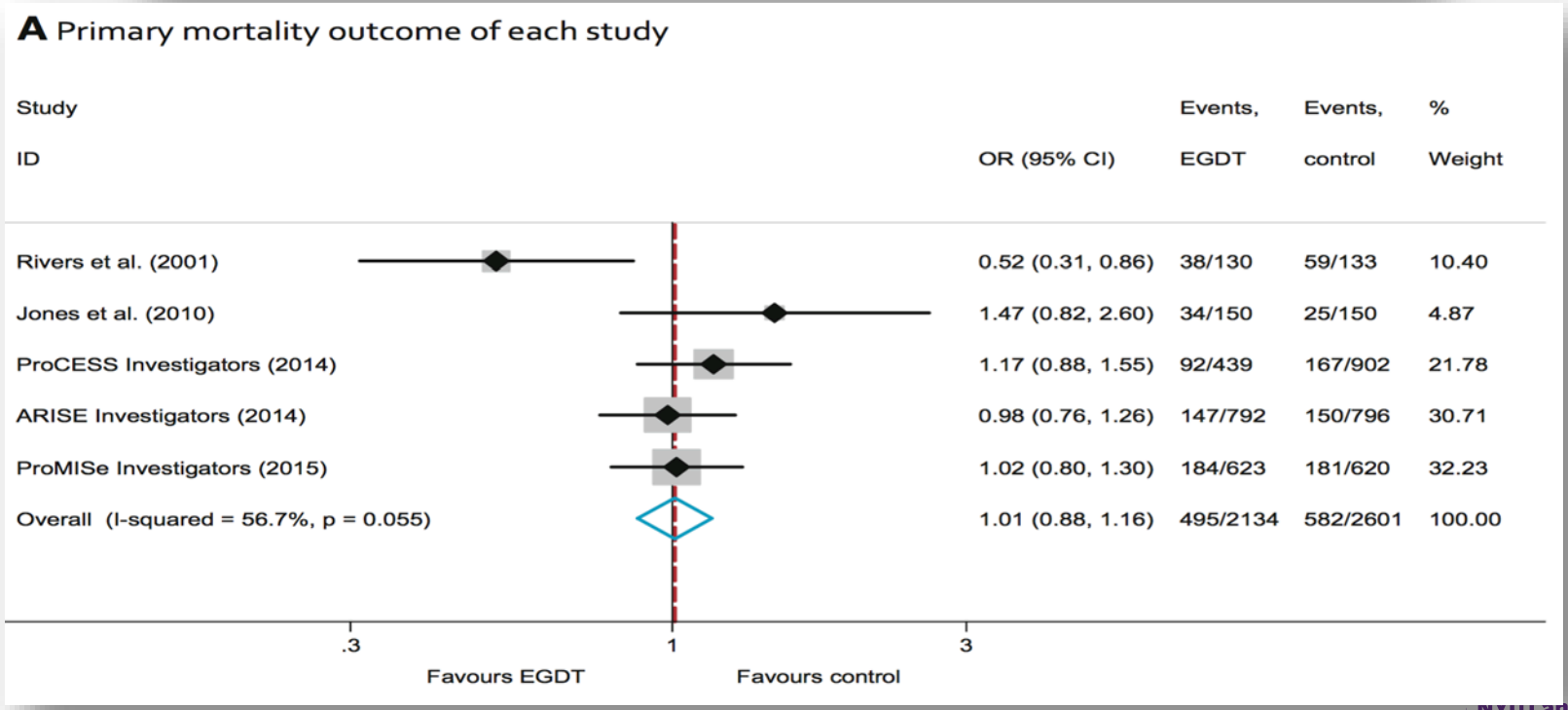
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators



Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

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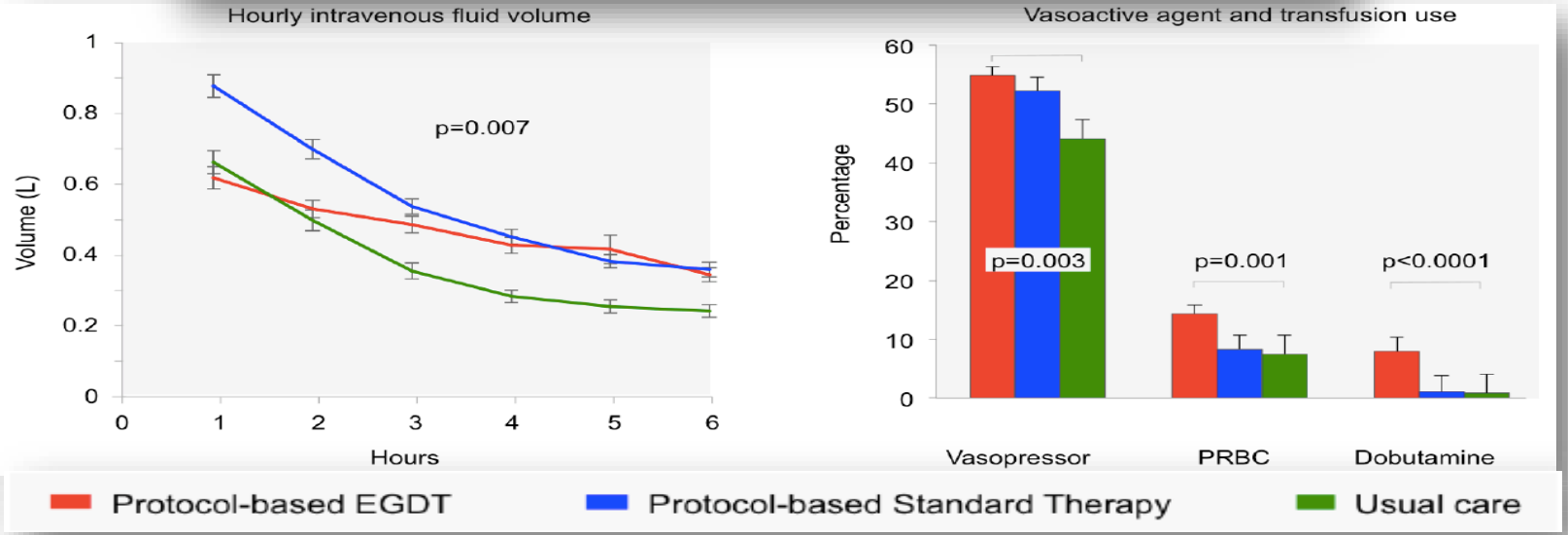
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*



Intravenous Fluids	
EGDT	2.8 L
Usual Care	2.3 L

Intravenous Antibiotics	
EGDT	97.5%
Usual Care	96.9%

DOI: 10.1056/NEJMoa1401602

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Caveats / Limitations of ProCESS, ARISE & Promise

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

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The River's work was useful….

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

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

(Best Practice Statement)

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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)

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Antibiotics within 1 hour: Evidence Profile

Quality assessment							Impact	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality at hospital discharge (Kumar logistic regression model (follow up: discharge)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Adjusted Odds Ratio 1.119 [1.103, 1.136] per hour delay in initiation of effective antimicrobial therapy after onset of hypotension.	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality, adjusted, based on time receiving antibiotics after time of presentation with severe sepsis criteria (Ferrer)									
1	observational studies	not serious	not serious	not serious	not serious	dose response gradient	Stratified by hour of receiving antibiotics, an increase in OR at each hour: 0-1: 1.00, 1-2: 1.07 [0.97, 1.18], 2-3: 1.14 [1.02, 1.26], 3-4: 1.19 [1.04, 1.35], 4-5: 1.24 [1.06, 1.45], 5-6: 1.47 [1.22, 1.76], >6: 1.52 [1.36, 1.70] [1]	⊕⊕⊕◯ MODERATE	CRITICAL

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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)

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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)

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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).

- **We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock**

(Weak recommendation, low quality of evidence).

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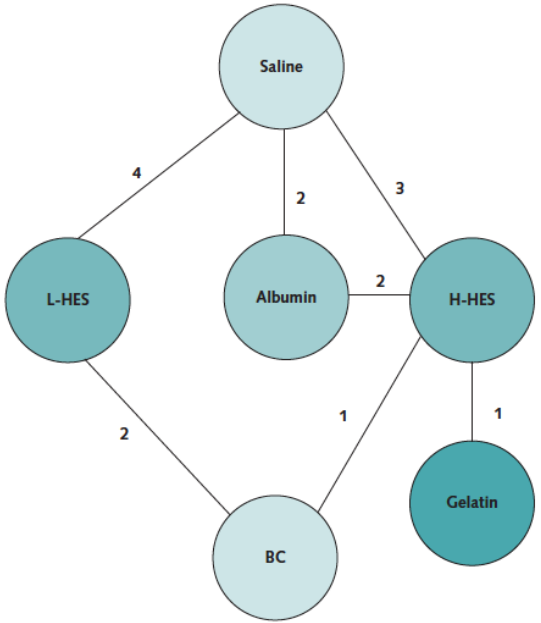
No direct comparisons in patients with sepsis

Appendix Figure 2. **Network map for 6-node analysis.**



BC = balanced crystalloid; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch.

Rochwerg et al Ann Intern Med. 2014;161:347-355.

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Table 4. **NMA Results of 6-Node Analysis, Including Confidence Assessments**

Comparison	Trials With Direct Comparisons, *n*	Direct Estimate (95% CI); Quality of Evidence	Indirect Estimate (95% CrI); Quality of Evidence	NMA Estimate (95% CrI)*; Quality of Evidence
L-HES vs. saline	4	1.07 (0.89–1.29); moderate†	0.59 (0.25–1.35); very low†‡§	1.04 (0.87–1.25); moderate
H-HES vs. saline	3	0.64 (0.30–1.37); moderate†	1.13 (0.71–1.80); very low†‡	0.95 (0.64–1.41); moderate
Albumin vs. saline	2	0.81 (0.64–1.03); moderate†	0.96 (0.14–6.31); very low†‖	0.82 (0.65–1.04); moderate
Balanced crystalloid vs. saline	0	–	0.78 (0.58–1.05); low†‡	0.78 (0.58–1.05); low
Gelatin vs. saline	0	–	1.04 (0.46–2.32); very low†‡	1.04 (0.46–2.32); very low
H-HES vs. L-HES	0	–	0.91 (0.63–1.33); low†‡	0.91 (0.63–1.33); low
Albumin vs. L-HES	0	–	0.79 (0.59–1.06); low†‡	0.79 (0.59–1.06); low
Balanced crystalloid vs. L-HES	2	0.80 (0.61–1.04); moderate§	0.44 (0.19–0.97); moderate‡	0.75 (0.58–0.97); moderate
Gelatin vs. L-HES	0	–	1.00 (0.44–2.21); very low†‡	1.00 (0.44–2.21); very low
Albumin vs. H-HES	2	1.40 (0.35–5.56); low‖	0.83 (0.52–1.33); low†‡	0.87 (0.55–1.36); low
Balanced crystalloid vs. H-HES	1	0.74 (0.52–1.05); moderate†	1.35 (0.63–2.92); very low‡‖	0.82 (0.60–1.13); moderate
Gelatin vs. H-HES	1	1.09 (0.55–2.19); low‖	–	1.10 (0.54–2.21); low
Balanced crystalloid vs. albumin	0	–	0.95 (0.65–1.38); very low†‡	0.95 (0.65–1.38); very low
Gelatin vs. albumin	0	–	1.26 (0.55–2.90); very low‡‖	1.26 (0.55–2.90); very low
Gelatin vs. balanced crystalloid	0	–	1.34 (0.61–2.89); very low‡‖	1.34 (0.61–2.89); very low

Rochwerg et al Ann Intern Med. 2014;161:347-355.

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shock requiring vasopressors.
(Strong recommendation; moderate quality of evidence)

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

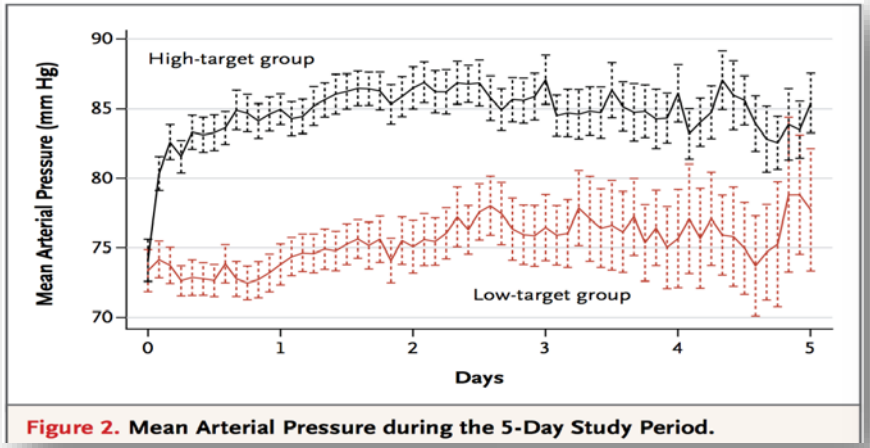

Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

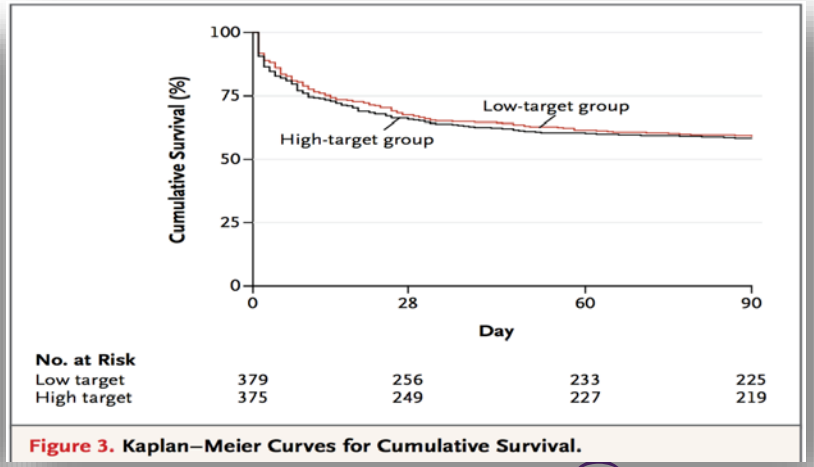

Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

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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)

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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)

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Lactate can help guide resuscitation

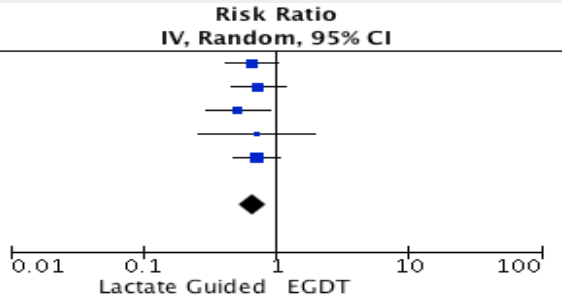
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

(Weak recommendation, low quality of evidence)

Study or Subgroup	Lactate Guided Events	Lactate Guided Total	Standard Events	Standard Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	34	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 3.51 (P = 0.0004)



Resuscitation 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.

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Sepsis Screening and Performance Improvement

- **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)

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Sepsis Performance Improvement

- Performance improvement efforts for sepsis are associated with improved patient outcomes
- 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

Damiani E et al. PLoS ONE 10(5): e0125827 (2015). doi:10.1371/journal.pone.0125827

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Diagnosis

- **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.**
  - **Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).**

(Best Practice Statement)

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Definitions for Antibiotic Therapy

Empiric therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification. Empiric therapy may be mono-, combination, or broad-spectrum, and/or multidrug in nature.
Targeted/definitive therapy	Therapy targeted to a specific pathogen (usually after microbiologic identification). Targeted/definitive therapy may be mono- or combination, but is not intended to be broad-spectrum.
Broad-spectrum therapy	The use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, usually during empiric therapy (e.g., piperacillin/tazobactam, vancomycin, and anidulafungin; each is used to cover a different group of pathogens). Broad-spectrum therapy is typically empiric since the usual purpose is to ensure antimicrobial coverage with at least one drug when there is uncertainty about the possible pathogen. On occasion, broad-spectrum therapy may be continued into the targeted/definitive therapy phase if multiple pathogens are isolated.
Multidrug therapy	Therapy with multiple antimicrobials to deliver broad-spectrum therapy (i.e., to broaden coverage) for empiric therapy (i.e., where pathogen is unknown) or to potentially accelerate pathogen clearance (combination therapy) with respect to a specific pathogen(s) where the pathogen(s) is known or suspected (i.e., for both targeted or empiric therapy). This term therefore includes combination therapy.
Combination therapy	The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a β-lactam for pneumococcal pneumonia).

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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)

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Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	doublecoverage antibiotic agents	monotherapy	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
28	observational studies	not serious	not serious	not serious	not serious	none	Although datasets with lower mortality/clinical failure rates demonstrated a nonsignificant increased mortality with combination therapy, this increased as that rate increased, such that at a mortality/clinical failure rate of >25%, the OR for dual therapy= 0.54 [0.45,0.66].				⨁⨁◯◯ LOW	CRITICAL
ICU mortality, consolidated dataset of combined shock and critically ill patients												
12	observational studies	not serious	not serious	not serious	not serious	strong association	N/A	N/A	OR 0.51 (0.36 to 0.72)	N/A	⨁⨁⨁◯ MODERATE	CRITICAL
Survival by meta-regression, dual therapy, per 10% increase in monotherapy group mortality												
62	observational studies	not serious	not serious	not serious	not serious	strong association	The probability of combination therapy having a beneficial effect increases for every 10% increase in monotherapy group mortality in the datasets. OR 1.318 [1.190-1.460].				⨁⨁⨁◯ MODERATE	CRITICAL
Mortality, propensity-matched analysis (follow up: 28 days)												
1	observational studies	not serious	not serious	not serious [6]	not serious	none	355/1223 (29.0%)	444/1223 (36.3%)	HR 0.77 (0.67 to 0.88)	70 fewer per 1,000 (from 35 fewer to 102 fewer)	⨁⨁◯◯ LOW	CRITICAL

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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)

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Antibiotic Stewardship

- **We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.** (Best Practice Statement)
- **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)

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Antibiotic Stewardship

- **We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.** (Best Practice Statement)
- **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)

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Corticosteroids

- **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)

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Glucose Control

- **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)

- **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.**

  (Best Practice Statement)

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Glucose Control

- **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.**

  (Best Practice Statement)

- **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)

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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)

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Summary of Initial Management

- Continued and enhanced emphasis on:
  - Early recognition
  - Immediate intervention with
    - Appropriate antibiotics
    - IV fluid
  - Frequent reassessment
    - No specific guidance on how

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Thank You

Question 1

In patients with septic shock, if fluid resuscitation does not restore adequate mean arterial pressure, the first choice vasopressor is:

A. Epinephrine
B. Vasopressin
C. Norepinephrine
D. Phenylephrine
E. Dopamine

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Question 2

Antibiotics should be given for patients with sepsis:

A. Within 3 hours of recognition
B. As soon as possible after recognition
C. Within 1 hour of Emergency Department triage
D. Within 1 hour of the onset of hypotension
E. Within 3 hours for sepsis and 1 hour for septic shock

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