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Clinical Meeting & Exhibition

Updates in the Management of Septic Shock

Jeremy DeGrado, Pharm.D., BCCCP, BCPS
Medical ICU Clinical Pharmacy Specialist
Brigham and Women's Hospital
Boston, MA

Heather Torbic, Pharm.D., BCCCP, BCPS
Medical ICU Clinical Pharmacy Specialist
Cleveland Clinic
Cleveland, OH

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Learning Objectives

- Compare and contrast 2016 guidelines compared to 2012, specifically with regard to definitions and early goal-directed therapy.
- Given a patient case, describe various methods of hemodynamic assessment and possible pharmacotherapy options for support.
- Describe the impact of various regulations on local sepsis guideline and protocol development.
- Apply and interpret international guidelines.

Case

- KB is a 67 year old male (83 kg) who presents from an inpatient rehabilitation facility with AMS, T39.0°C, and BP 103/75. PMH significant for T2DM, ESRD on IHD, and underwent a left BKA 2 weeks ago for a non-healing foot ulcer.
- In the ED his HR is 117 beats/min, BP 85/58 mm Hg (MAP 67 mm Hg), Hgb 7.3 g/dL, Hct 23%, Na 144 mEq/L, K 4.8 mEq/L, Cl 112 mEq/L, and lactate 4.1 mmol/L. There is a foul odor and green discharge coming from the incision site on his left leg.

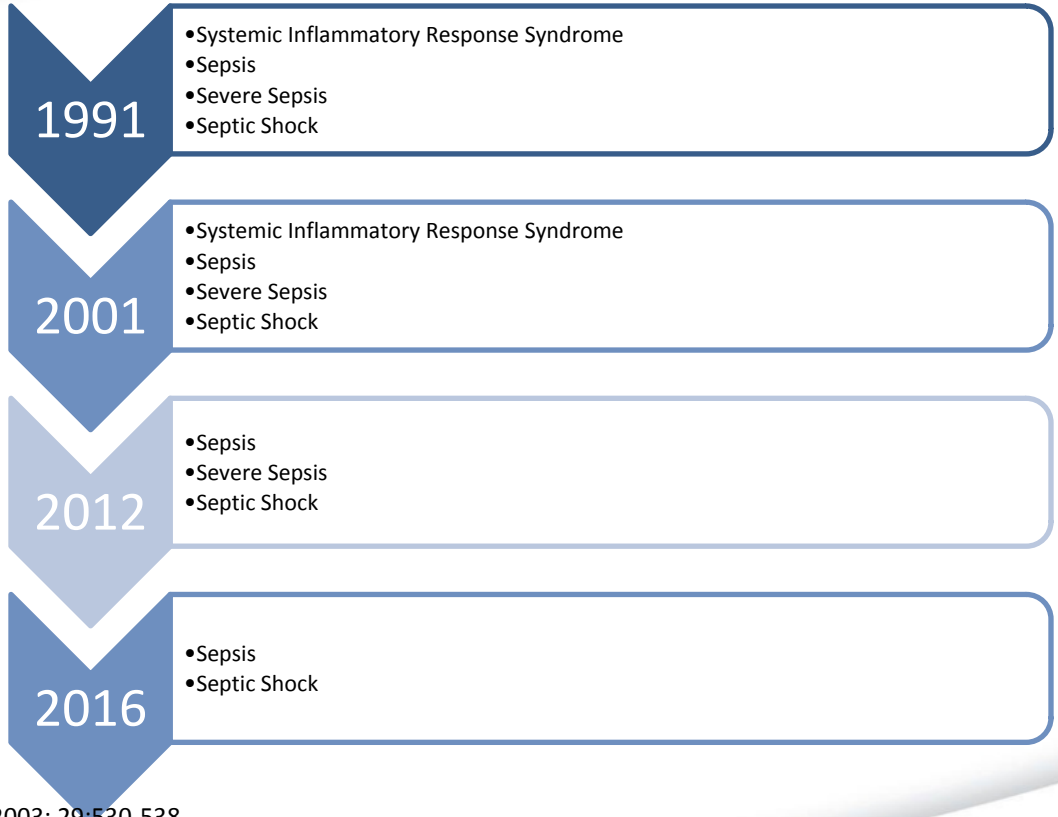
- Does KB have SIRS, sepsis, severe sepsis, or septic shock?

Sepsis

- Leading cause of mortality and critical illness worldwide
- Septic shock
  - Incidence: 19 cases/1000 hospitalizations
  - Mortality: 40-50%
- 2011 - $20 billion of US hospital costs
- CMS Core Measure affecting reimbursement
- Survivors often suffer from long-term sequelae

Singer M, et al. *JAMA*. 2016;315(8):801-810.
Kadri SS, et al. *Chest*. 2017;151(2):278-285.

Evolving Sepsis Definitions



Levy MM, et al. *Intensive Care Med.* 2003; 29:530-538.
Dellinger RP, et al. *Crit Care Med.* 2013; 41:580-637.
Singer M, et al. *JAMA*. 2016;315(8):801-810.

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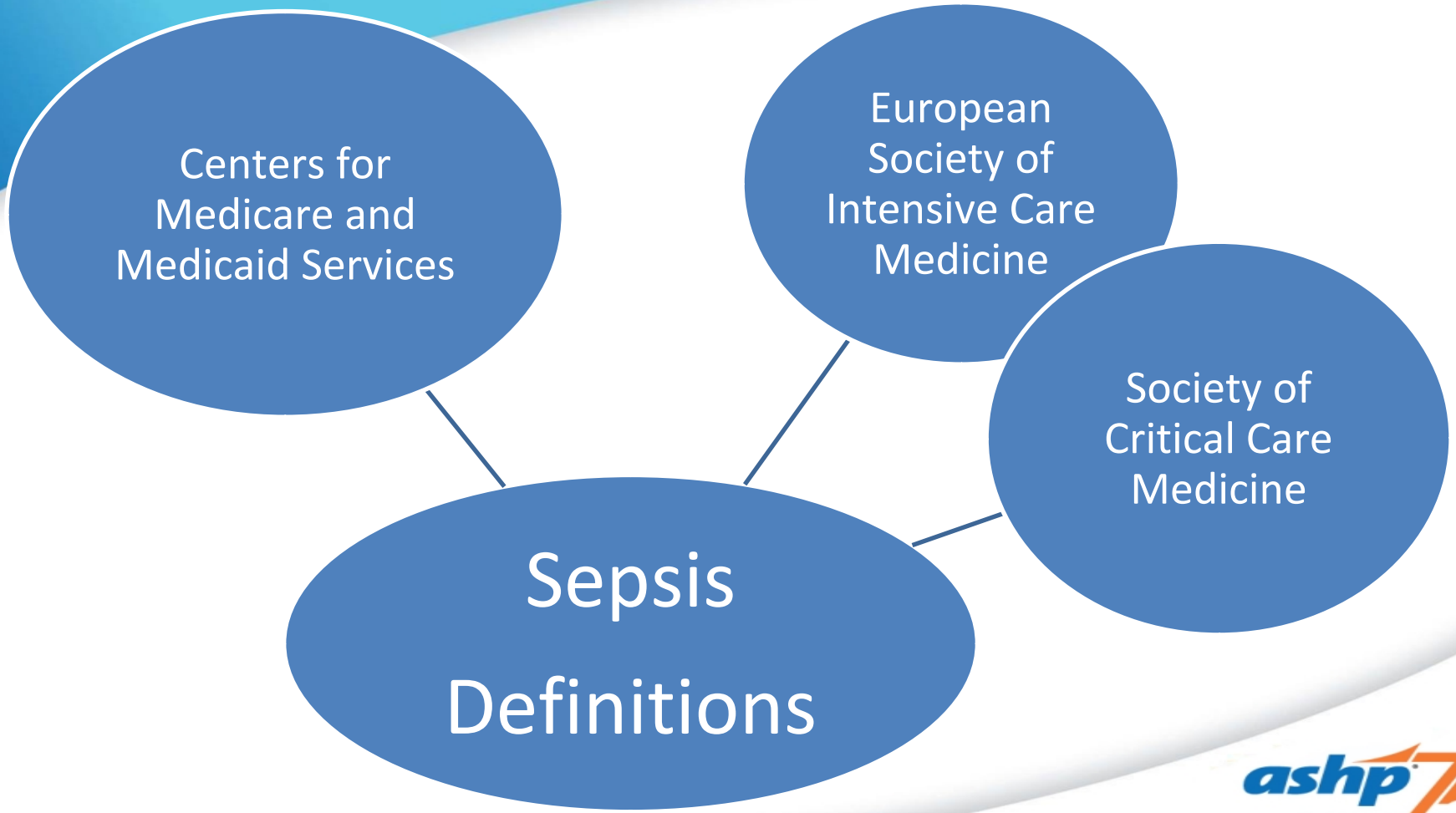
Centers for Medicare and Medicaid Services
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Society of Critical Care Medicine
Sepsis Definitions

SEPSIS-3 Sepsis Definition

- Suspected/documented infection plus:
  - Acute increase of ≥ 2 Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score points

- Quick SOFA(qSOFA)
  - RR ≥ 22 breaths/min
  - Altered mentation
  - SBP ≤ 100 mmHg

*If ≥ 2 qSOFA points exist, evaluate for organ failure

Singer M, et al. *JAMA*. 2016;315(8):801-810.

SEPSIS-3 Septic Shock Definition

- Sepsis plus:
  - Persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg

-AND-

  - Blood lactate >2 mmol/L despite adequate volume resuscitation

Singer M, et al. *JAMA*. 2016;315(8):801-810.

CMS SEP-1 Definitions

Sepsis	Suspected infection + ≥ 2 SIRS criteria
Severe Sepsis	Sepsis + lactate > 2 or ≥ 1 variable of organ dysfunction
Septic Shock	Severe sepsis + lactate > 4 or hypoperfusion despite fluid resuscitation

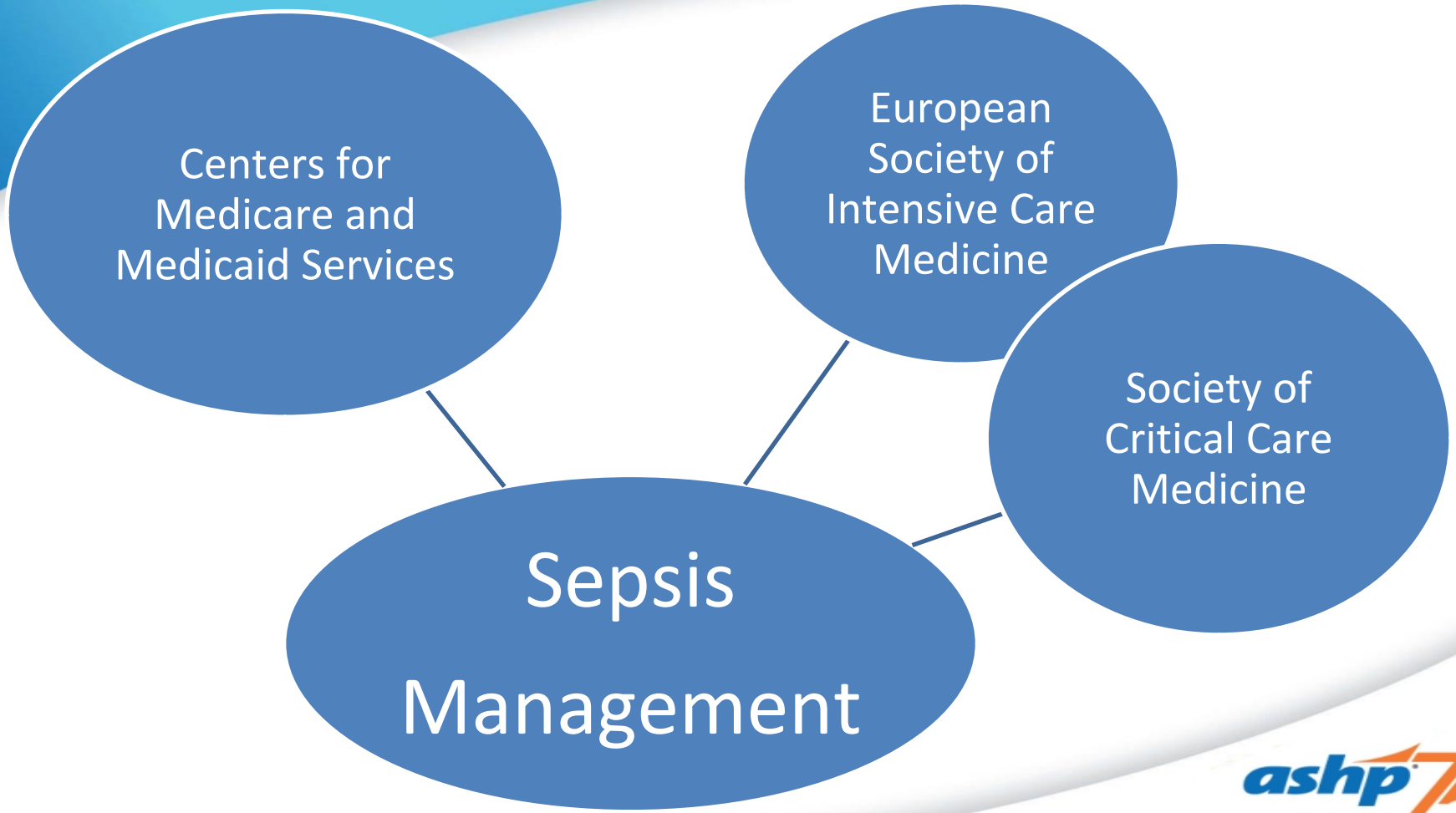
Organ dysfunction variables:
SBP < 90, MAP < 70, SBP decrease > 40 from baseline, Scr > 2, UOP < 0.5 ml/kg/hr > 2 hr, bilirubin > 2, platelets < 100,000, INR > 1.5, PTT > 60, altered mental status

Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

Case

- KB is a 67 year old male (83 kg) who presents from an inpatient rehabilitation facility with AMS, T39.0°C, and BP 103/75. PMH significant for T2DM, ESRD on IHD, and underwent a left BKA 2 weeks ago for a non-healing foot ulcer.
- In the ED his HR is 117 beats/min, BP 85/58 mm Hg (MAP 67 mm Hg), Hgb 7.3 g/dL, Hct 23%, Na 144 mEq/L, K 4.8 mEq/L, Cl 112 mEq/L, and lactate 4.1 mmol/L. There is a foul odor and green discharge coming from the incision site on his left leg.
- Does KB have SIRS, sepsis, severe sepsis, or septic shock?

	SEPSIS-3	CMS SEP-1
Sepsis	Quick SOFA(qSOFA) -RR ≥ 22 breaths/min -Altered mentation -SBP ≤ 100 mmHg ✓	Suspected infection + ≥ 2 SIRS criteria ✓
Severe Sepsis	n/a	Sepsis + lactate > 2 or ≥ 1 variable of organ dysfunction ✓
Septic Shock	Sepsis + Hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg + Lactate >2 mmol/L despite adequate volume resuscitation	Severe sepsis + lactate > 4 or hypoperfusion despite fluid resuscitation ✓


Centers for Medicare and Medicaid Services
European Society of Intensive Care Medicine
Society of Critical Care Medicine
Sepsis Management

Early Goal Directed Therapy

Study design	Single center prospective randomized controlled trial	
Patients	Adults presenting to the ED with severe sepsis, septic shock, or the sepsis syndrome	
Interventions	Arterial and central venous catheterization	
	Standard therapy • CVP ≥ 8-12 mm Hg • MAP ≥ 65 mm Hg • UOP ≥ 0.5 ml/kg/hr	EGDT ≥ 6 h & continuous $ScvO_2$ monitoring • CVP ≥ 8-12 mm Hg • MAP ≥ 65 mm Hg • UOP ≥ 0.5 ml/kg/hr • $ScvO_2$ ≥ 70 %
Results	• In-hospital mortality: EGDT 30.5% vs. Control 46.5%, P=0.009 • Resuscitation endpoints favored EGDT	

Rivers E, et al. *N Engl J Med.* 2001; 345(19):1368-1377.

Early Goal Directed Therapy

	ProCESS	ARISE	PROMISE
Methods	EGDT vs. Protocol vs. Usual Care	EGDT vs. Usual Care	EGDT vs. Usual Care
Results	•60-day Mortality: 21.0% vs. 18.2% vs. 18.9% (p=0.83) •More renal failure in protocol group (p=0.04)	•90-day Mortality: 18.6% vs. 18.8% (p=0.90) •More vasopressor use in EGDT group	•90-day Mortality: 29.5% vs. 29.2% (p=0.90) •More fluids and vasopressor use in EGDT group
Conclusion	•No mortality benefit with EGDT •Patients randomized to EGDT received more invasive monitoring, more fluids/PRBC/vasopressors, and more advanced support		

Yealy DM, et al. *N Engl J Med.* 2014; 370:1683-1693.
ARISE investigators. *N Engl J Med.* 2014; 371:1496-1506.
Mouncey PR, et al. *N Engl J Med.* 2015; 372:1301-1311.

Surviving Sepsis Campaign Guidelines

2012

- Early goal directed therapy
- Sepsis bundles/ protocolized care

2016

- Early recognition, treatment, and reassessment
- Decreased emphasis on EGDT and protocolized care
- More comprehensive antimicrobial recommendations

Dellinger RP, et al. *Crit Care Med.* 2013; 41:580-637.
Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

CMS SEP-1 Guidelines

	Severe Sepsis	Septic Shock
Within 3 hours of presentation	• Measure lactate • Obtain cultures prior to antibiotics • Administer antibiotics	• Measure lactate • Obtain cultures prior to antibiotics • Administer antibiotics • Administer 30 mL/kg crystalloids
Within 6 hours of presentation	• Repeat lactate if initial is > 2	• Repeat volume status and tissue perfusion assessment • Administer vasopressors (if still hypotensive after fluids)

Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

CMS SEP-1 Guidelines

Included Populations	Excluded Populations

• Age ≥ 18 years old
• ICD-10 Code:
  • Sepsis
  • Severe Sepsis
  • Septic Shock
	• Comfort Care Directive
	  • Within 3 hours of severe sepsis
	  • Within 6 hours of septic shock
	• Length of stay > 120 days
	• Transfer from outside acute care facility
	• Death
	  • Within 3 hours of severe sepsis
	  • Within 6 hours of septic shock

Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

SSC Guidelines
Fluid Selection

- Best Practice Recommendations
  - Use fluid challenge technique as long as hemodynamics continue to improve
- Strong Recommendations
  - Crystalloids for initial resuscitation and subsequent volume replacement
  - Avoid hydroxyethyl starches
- Weak Recommendations
  - Balanced crystalloids or saline for initial resuscitation
  - Albumin for initial resuscitation if requiring substantial amounts of crystalloids

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

Fluid Selection

SSC Guidelines	CMS SEP-1

• Crystalloids for initial resuscitation and subsequent volume replacement
• Avoid hydroxyethyl starches
• Balanced crystalloids or saline for initial resuscitation
• Albumin for initial resuscitation if requiring substantial amounts of crystalloids
	• Resuscitation with 30 ml/kg of crystalloid therapy only
	  • Initiated within 3 hours of presentation with septic shock
	  • Actual body weight
	  • Infusion rate ≥ 125 ml/hr

Rhodes A et al. *Crit Care Med.* 2017; (43)3:304-377.
Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

Choice of Fluid

Crystalloids	Colloids	Balanced	Unbalanced
• Sodium chloride 0.9% • Lactated Ringers • Hypertonic saline	• Modified gelatins • Dextran • Albumin • Hydroxyethyl starches	• Lactated Ringers • Plasma-Lyte • Hartmann's solution	• Sodium chloride 0.9% • Colloids • Hypertonic saline

Finfer S et al. *N Engl J Med*. 2004; 350(22):2247-2256.
Perel P, Roberts I, Ker K. *Cochrane Database Syst Rev*. 2013; 2:CD000567.
Morgan TJ. *Curr Opin Crit Care*. 2013; 19(4):299-307.

Crystalloids vs. Colloids

- No evidence that colloids are better than crystalloids for fluid resuscitation in ICU, trauma, burn, or postoperative patients
  - Mortality
  - Pulmonary edema
  - Length of stay
- Larger well-designed randomized trials are needed to achieve sufficient power to detect potentially small differences in treatment effects if they truly exist

Choi PT, et al. *Crit Care Med.* 1999; 27:200-210.
Perel P, Roberts I, Ker K. *Cochrane Database Syst Rev*. 2013; 2:CD000567.

SAFE Study

Methods	• Adult ICU patients requiring fluids to maintain/increase intravascular volume • 4% albumin vs. Sodium chloride 0.9%
Results	• Mortality: Albumin 726 deaths v. 729 deaths; Relative risk of death 0.99; 95% CI 0.91-1.09; P=0.87 • No difference in new organ failure, need for renal replacement therapy, duration of mechanical ventilation, and ICU or hospital length of stay

SAFE Study – Subgroup Analysis

Subgroup	4% Albumin	Sodium Chloride 0.9%	Relative Risk (95% CI)	P value
Trauma	81/596 (13.6%)	59/590 (10.0%)	1.36 (0.99-1.86)	0.006
Severe sepsis	185/603 (30.7%)	217/615 (35.3%)	0.87 (0.74-1.02)	0.09
Acute respiratory distress syndrome	24/61 (39.3%)	28/66 (42.4%)	0.93 (0.61-1.41)	0.72

SAFE study investigators. *N Engl J Med.* 2004; 350(22):2247-2256.

ALBIOS Study

Is there a mortality benefit when maintaining serum albumin levels ≥ 3.0 g/dL in patients with severe sepsis?

Methods	• Adult ICU patients with severe sepsis • 20% albumin + crystalloid to maintain albumin ≥ 3.0 g/dL vs. crystalloid
Results	• 28-Day Mortality: Albumin 31.8% vs. Crystalloid 32.0%; Relative risk of death 1.00; 95% CI 0.87-1.14; P=0.94 • Albumin group had a higher MAP (P=0.03) and lower net fluid balance (P<0.001) in the first 7 days • No difference in 90-day mortality, new organ failure, need for renal replacement therapy, duration of mechanical ventilation, and ICU or hospital length of stay

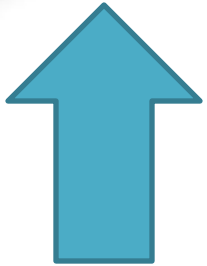
ALBIOS investigators. *N Engl J Med.* 2014; 370:1412-1421.

Balanced vs. Unbalanced Fluids

- Unbalanced fluids routinely used for initial resuscitation in sepsis
  - May induce hyperchloremia and metabolic acidosis
- Balanced fluids more similar electrolyte composition to plasma
  - Associated with reduced perioperative mortality and ICU morbidity

Neyra JA, et al. *Crit Care Med*. 2015; 43:1938-1944.
Shaw AD, et al. *Intensive Care Med*. 2014; 40:1897-1905.
Zampieri, FG et al. *Crit Care Med*. 2016; 44:2163-2170.

Hyperchloremia

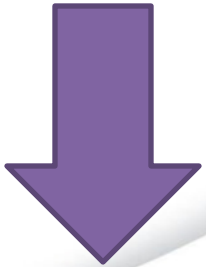


Hyperchloremia (Cl ≥ 110 mEq/L) at admission and persisting at ICU day 3 associated with increased mortality

- OR 1.38; 95%CI 1.13-1.68; p=0.002

Resuscitation with lower Cl load is associated with lower mortality

- 3.5% (Δ0-10 mmol/L) vs. 9.7% (Δ30-40 mmol/L), p<0.001



Neyra JA, et al. *Crit Care Med*. 2015; 43:1938-1944.
Shaw AD, et al. *Intensive Care Med*. 2014; 40:1897-1905.
Zampieri FG, et al. *Crit Care Med*. 2016; 44:2163-2170.

Balanced vs. Unbalanced Fluids

	SPLIT Trial	Sepsis Trial
Methods	• ICU patients requiring crystalloids • Sodium chloride 0.9% vs. Plasma-Lyte 148	• Nonsurgical ICU patients with sepsis • Balanced vs. unbalanced fluids
Results	• No difference in incidence of acute kidney injury (including sepsis subgroup) • No difference in incidence of renal replacement therapy, duration of mechanical ventilation, ICU and hospital lengths of stay, and in-hospital mortality	• Balanced fluids were associated with a significantly decreased in-hospital mortality (19.6 vs. 22.8%, RR 0.86, p=0.001) • No significant difference in incidence of acute renal failure and ICU or hospital lengths of stay

Young P, et al. *JAMA*. 2015; 314(16):1701-1710.
Raghunathan, et al. *Crit Care Med*. 2014; 42:1585-1591.

Case

- KB is a 67 year old male (83 kg) who presents from an inpatient rehabilitation facility with AMS, T39.0°C, and BP 103/75. PMH significant for T2DM, ESRD on IHD, and underwent a left BKA 2 weeks ago for a non-healing foot ulcer.
- In the ED his HR is 117 beats/min, BP 85/58 mm Hg (MAP 67 mm Hg), Hgb 7.3 g/dL, Hct 23%, Na 144 mEq/L, K 4.8 mEq/L, Cl 112 mEq/L, and lactate 4.1 mmol/L. There is a foul odor and green discharge coming from the incision site on his left leg.

- What is the best initial order for fluid resuscitation in KB?

A. Sodium chloride 0.9%, 1000 ml/hr x 2.5 L
B. Lactated Ringers, 1000 ml/hr x 2.5 L
C. Lactated Ringers 100 ml/hr x 2.5 L
D. Sodium Chloride 0.9%, 1000 ml/hr x 1L

Case

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C. Lactated Ringers 100 ml/hr x 2.5 L
D. Sodium Chloride 0.9%, 1000 ml/hr x 1L

Antibiotic Timing

Increased in-hospital mortality with each hour delay in administration of effective antibiotics

Time to antibiotics (hour)	OR	95% CI	P value	Probability of mortality (%)	95% CI
0-1	1.00			24.6	23.2-26.0
1-2	1.07	0.97-1.18	0.165	25.9	24.5-27..2
2-3	1.14	1.02-1.26	0.021	27.0	25.3-28.7
3-4	1.19	1.04-1.35	0.009	27.9	25.6-30.1
4-5	1.24	1.06-1.45	0.006	28.8	25.9-31.7
5-6	1.47	1.22-1.76	<0.001	32.3	28.5-36.2
>6	1.52	1.36-1.70	<0.001	33.1	30.9-35.3

Ferrer R, et al. *Crit Care Med*. 2014; 42:1749-1755.

SSC Guidelines
Antimicrobial Therapy

- Best Practice Recommendations
  - Obtain appropriate routine microbiologic cultures prior to initiating antimicrobial therapy if doing so does not does not result in substantial delay in the start of antimicrobials
  - Utilize PK/PD principles to optimize therapy
  - No sustained prophylaxis for noninfectious inflammatory states
  - Achieve source control as soon as possible
  - If combination therapy is initially used, de-escalate in response to clinical improvement and culture data

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

SSC Guidelines
Antimicrobial Therapy

- Strong Recommendations
  - Administer IV antimicrobials as soon as possible and within 1 hour recognition of sepsis
  - Empiric broad-spectrum therapy
- Weak Recommendations
  - Combination therapy aimed at most likely pathogen for initial management of septic shock
  - Combination therapy not routine for ongoing treatment of serious infections, including bacteremia and sepsis without shock
  - Procalcitonin levels to support decreasing duration
  - Duration 7-10 days appropriate for most infections

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

Antimicrobial Therapy

SSC Guidelines	CMS SEP-1

• Obtain cultures prior to initiating antimicrobial therapy if doing so does not does not result in substantial delay in the start of antimicrobials
• Administer IV antimicrobials as soon as possible and within 1 hour recognition of sepsis
• Empiric broad-spectrum therapy
	• Within 3 hours of presentation:
	  • Blood cultures drawn prior to antibiotics
	  • Broad spectrum or other antibiotics administered

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.
Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

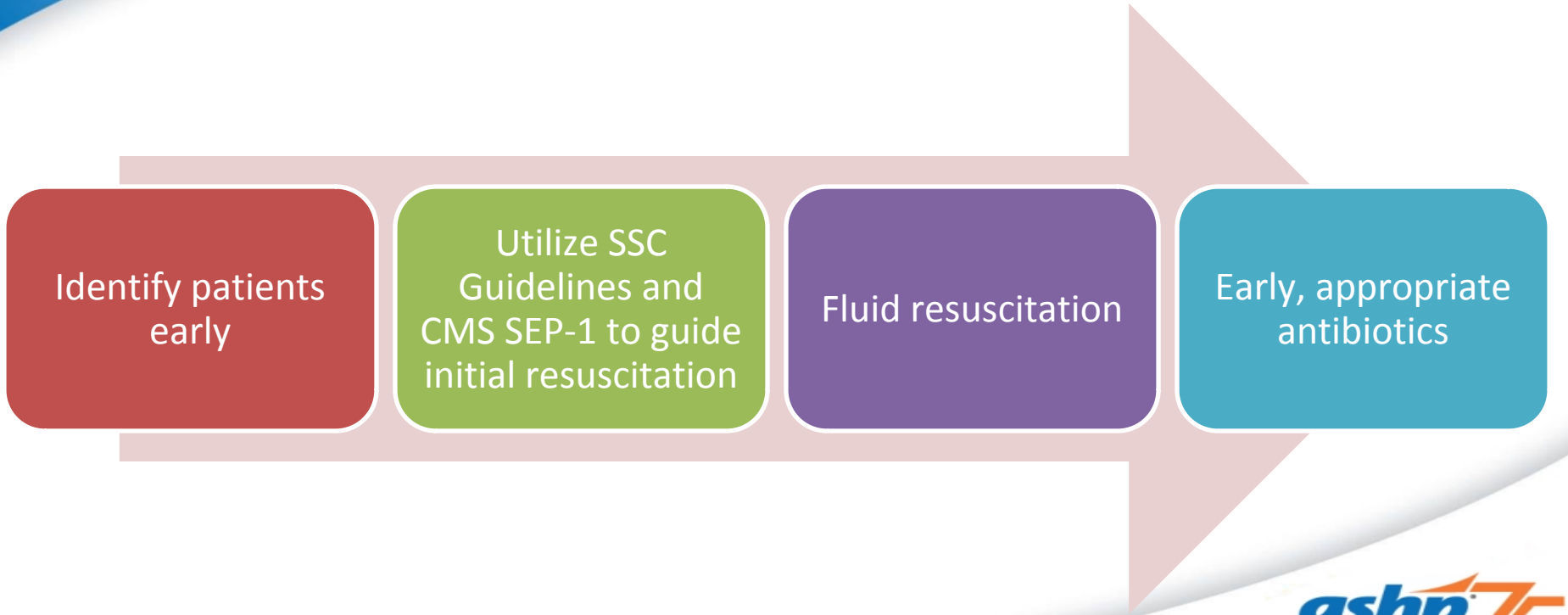
CMS SEP-1

Recommended Antimicrobial Therapy

Monotherapy	OR	Column A	AND	Column B
Doripenem		Amikacin		Cefazolin
Ertapenem		Gentamicin		Cefoxitin
Imipenem/Cilastatin		Tobramycin		Cefuroxime
Meropenem		Aztreonam		Clindamycin
Cefotaxime		Ciprofloxacin		Daptomycin
Ceftazidime				Telavancin
Ceftriaxone				Vancomycin
Cefepime				Linezolid
Ceftaroline fosamil				Azithromycin
Moxifloxacin				Erythromycin
Levofloxacin				Ampicillin
Amoxicillin/clavulanate				Nafcillin
Ampicillin/sulbactam				Oxacillin
Piperacillin/tazobactam				Penicillin G

Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

To review…


Identify patients early
Utilize SSC Guidelines and CMS SEP-1 to guide initial resuscitation
Fluid resuscitation
Early, appropriate antibiotics

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Updates in the Management of Septic Shock

Jeremy DeGrado, Pharm.D., BCCCP, BCPS
Medical ICU Clinical Pharmacy Specialist
Brigham and Women's Hospital
Boston, MA

Heather Torbic, Pharm.D., BCCCP, BCPS
Medical ICU Clinical Pharmacy Specialist
Cleveland Clinic
Cleveland, OH

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Case

- KB has received 3 L crystalloid in the first 6 hours and now is mechanically ventilated on volume-control ventilation with TV 8-10 mL/kg. HR 120 bpm (SR), BP 95/55 (MAP 68) mm Hg, urine output 25-50 mL/hr, CVP 12, $ScvO_2$ 73%, lactate 3.2 mmol/L, Hct 29%

- *What is the best choice regarding further fluid resuscitation in KB?*

A. CVP is 12, further fluids should not be administered
B. Hct is 29%, PRBC should be administered
C. MAP is low, more fluids should be administered along with initiating norepinephrine
D. Passive leg raise maneuver should be performed

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Goals of Resuscitation

- Early, early, early
- Improve organ perfusion
  - Increase SV
  - Increase CO
- Volume status assessment
  - Determine fluid responsiveness
  - Avoid fluid overload
- Maintain adequate pressures
  - Hemodynamic assessment
  - Vasoactive agents, fluids, adjunctive support based on patient data

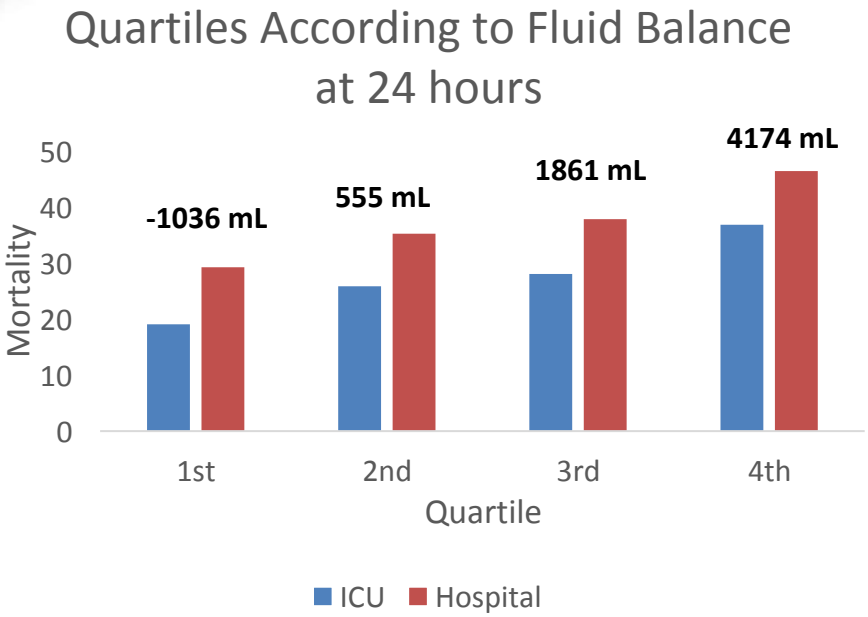
Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

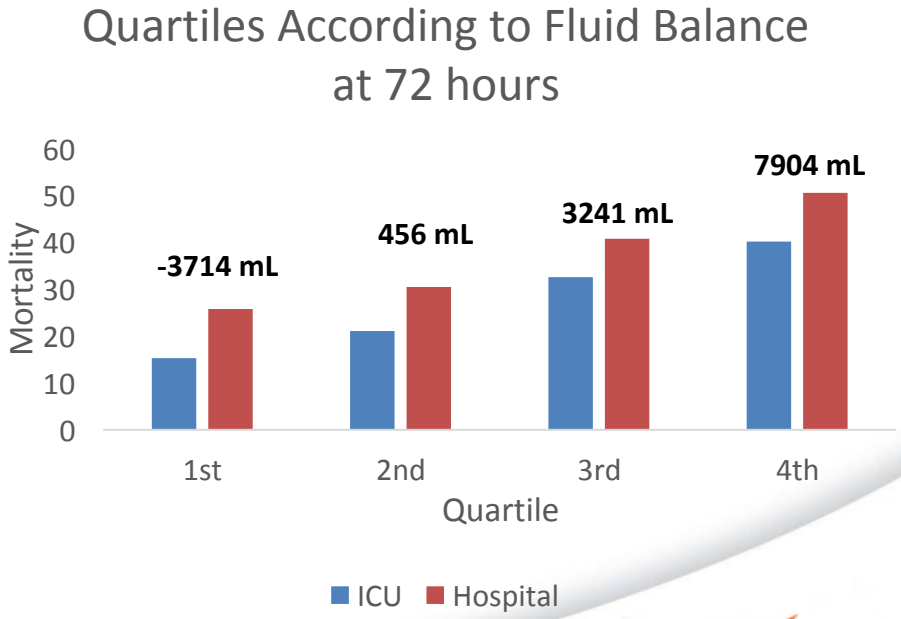
SSC Guidelines
Resuscitation

- Strong Recommendations
  - 30 ml/kg IV crystalloid within first 3 hours
  - Goal MAP > 65 mm Hg for patients in shock on vasopressors
- Weak Recommendations
  - Dynamic > static variables to predict fluid responsiveness
  - Normalize lactate

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

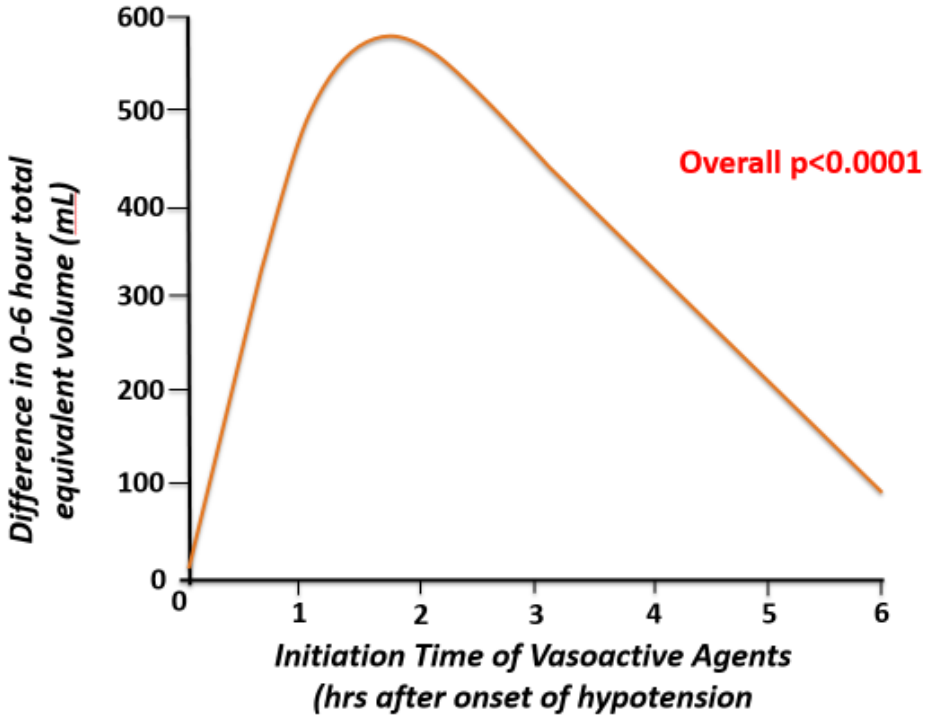
Fluid Balance and Mortality





Sakr Y, et al. *Crit Care Med*. 2017; 45(3):386-394.

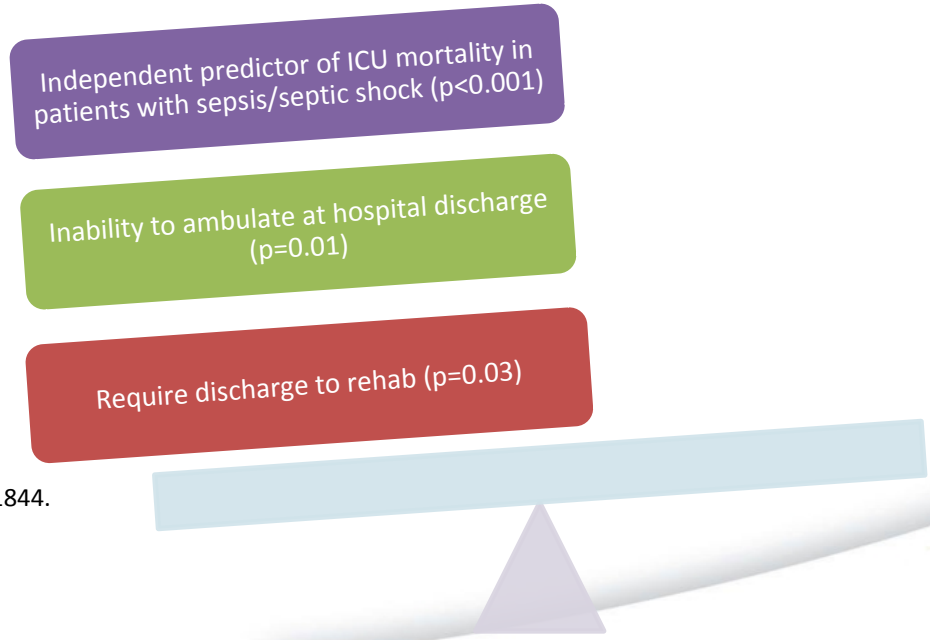
Fluid Administration and Vasopressor Initiation



Waechter J, et al. *Crit Care Med*. 2014; 42:2158-2168. (adapted)

Fluid Balance

Volume Overload



Mitchell KH, et al. *Ann Am Thorac Soc*. 2015; 12:1837-1844.
de Oliveira FS, et al. *J Crit Care*. 2015; 30:97-101.
Neyra JA, et al. *Crit Care Med*. 2016; 44:1891-1900.
Acheampong A, Vincent JL. *Crit Care*. 2015; 19:251.
Brotfain E, et al. *Am J Emerg Med*. 2016; 34:2122-2126.

Fluid Responsiveness

Static	Dynamic	Techniques
• Central venous pressure (CVP) • LV or RV end-diastolic volume • Pulmonary artery occlusion pressure	• Stroke volume variation (SVV) • Pulse pressure variation (PPV)	• Passive leg raise (PLR) • Fluid challenge • Tidal volume challenge

Marik PE, et al. *Ann Intensive Care* 2011; 1:1.
Myatra SN, et al. *Crit Care Med*. 2017; 45:415-421.

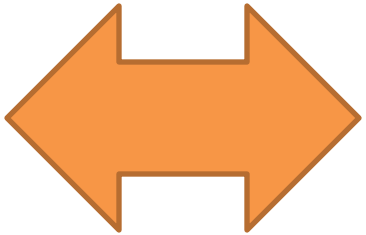
Assessing Volume Status

SSC Guidelines	CMS SEP-1	
• Reassessment should include thorough clinical exam and evaluation of available physiologic variables • Dynamic variables preferred to predict fluid responsiveness	Focused exam including: Vital signs **+** Cardiopulmonary exam **+** Capillary refill evaluation **+** Peripheral pulse evaluation **+** Skin exam	OR Any 2 of the following: - CVP - Central venous oxygen measurement - Bedside cardiovascular ultrasound - PLR or Fluid Challenge

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.
Available from: https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/core-measures.html

Lactate Guided Resuscitation

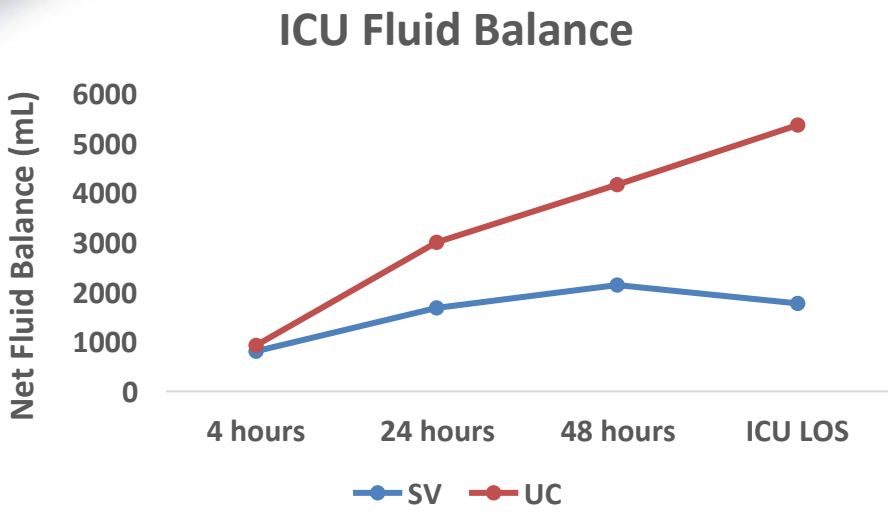
- Decreases mortality (RR 0.67; 95% CI 0.53-0.84)
- Benefit greatest in hospitals with higher baseline mortality



- No effect on ICU length of stay (mean difference -1.51 days; 95% CI -3.65-0.62)

Gu WJ, et al. *Intensive Care Med.* 2015; 41:1862-1863.
Simpson SQ, et al. *J Crit Care*. 2016; 36:43-48.

Stroke Volume-Guided Resuscitation



Multivariable Analysis

Outcome	Results	p-Value
Net fluid balance 4h	-361 mL	0.053
Net fluid balance 24h	-1392 mL	<0.001
Net fluid balance 48h	-1485 mL	0.004
In-hospital mortality, %	OR 0.58	0.25
ICU LOS (survivors), d	-2.55 days	0.04
Mechanically ventilated	OR 0.34	0.01
Ventilator days	-2.15 days	0.17
Vasopressor initiated	OR 0.57	0.15
Vasopressor duration	-27.94 hours	0.02

Latham HE, et al. *J Crit Care*. 2017;42:42-46.

Fluid Responsiveness

	CVP Meta-Analysis	PLR Meta-Analysis
Methods	• 22 studies (n=1148) • Divided CVP: <8, 8-12, >12 mm Hg	• 21 studies (n=991) • Assessed CO and arterial pulse pressure (PP)
Results	• Highest positive predictive value was 65% for all CVPs 0-20 mm Hg • Positive predictive value decreased as CVP increased	• PLR changes in CO: 85% sensitivity, 91% specificity • PLR changes in CO: 56% sensitivity, 83% specificity
Conclusion	• Positive predicative value was low for all CVP values assessed	• Changes in CO during a PLR test more reliably predict fluid responsiveness than change in arterial PP

Eskesen TG, et al. *Intensive Care Med*. 2016; 42(3):324-332.
Monnet X, et al. *Intensive Care Med*. 2016; 42(12):1935-1947.

Case

- KB is thought to no longer be fluid responsive, and was initiated on norepinephrine. The dose of norepinephrine has fluctuated between 5 and 10 mcg/min over last 8 hours.

- *What would you choose as your next step?*

A. Add vasopressin
B. Add epinephrine
C. Add hydrocortisone
D. Continue with current regimen

SSC Guidelines
Vasopressor Therapy

2012

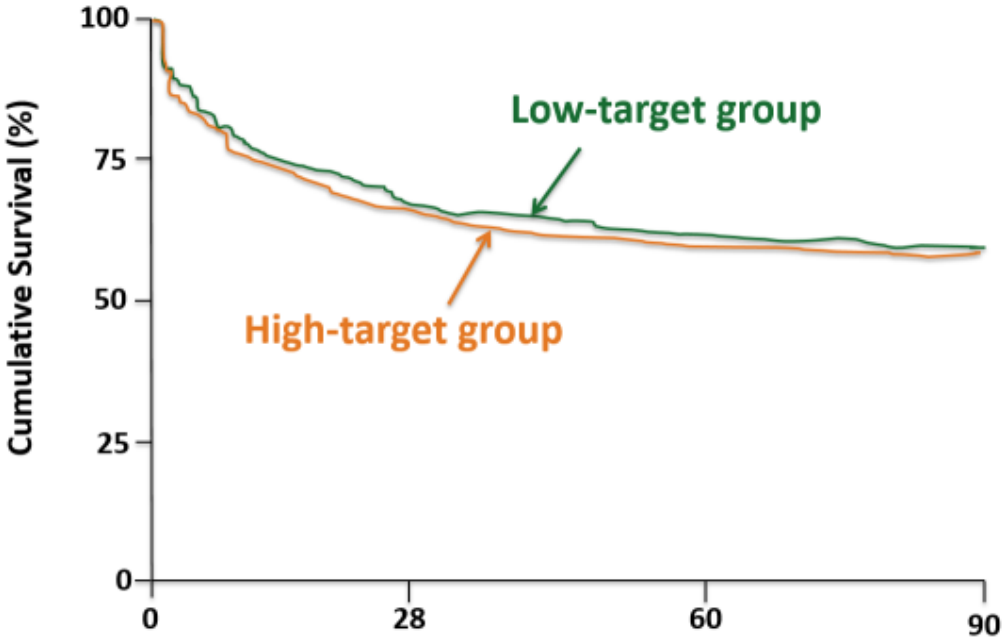
- Norepinephrine (NE) first-line vasopressor
- Add epinephrine to NE (or substitute for NE) when an additional agent to maintain MAP is needed
- Add vasopressin to NE to reach MAP goal or vasopressin to decrease NE dose
- Dopamine in select patients
- Phenylephrine if NE is associated with serious arrhythmias, CO is high but BP low, or as salvage therapy
- Dobutamine for hypoperfusion despite fluid resuscitation and vasopressors

2016

- Norepinephrine (NE) first-line vasopressor
- Add vasopressin or epinephrine to NE to reach MAP goal or vasopressin to decrease NE dose
- Dopamine in select patients
- No “renal-dose” dopamine
- Dobutamine for hypoperfusion despite fluid resuscitation and vasopressors

Dellinger RP, et al. *Crit Care Med.* 2013; 41:580-637.
Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

SEPSISPAM



No. at risk				
Low target	379	256	233	225
High target	375	249	227	219

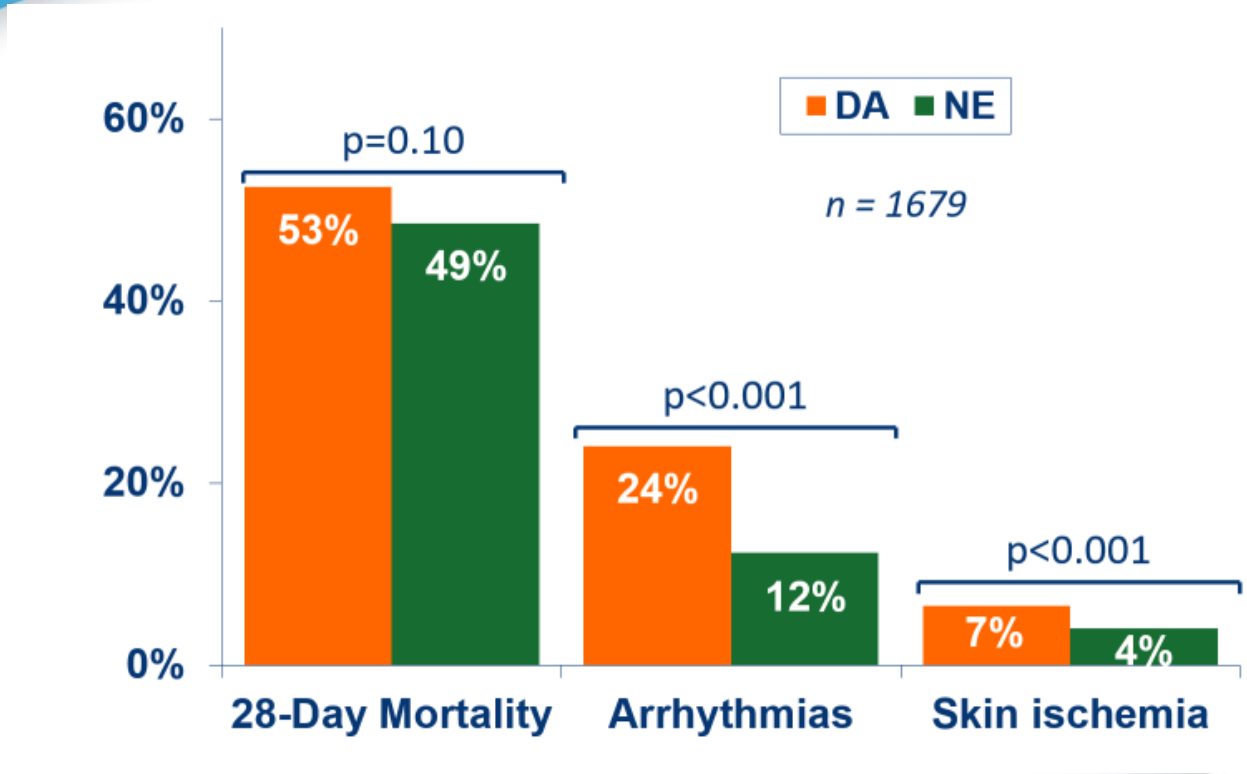
Asfar P, et al. *N Engl J Med.* 2014; 370:1583-1593.

OVATION Pilot

OVATION	
Patients	Vasodilatory shock requiring vasopressor therapy
Methods	Vasopressor titrated to MAP 75 to 80 mmHg (high-target) or 60 to 65 mmHg (low-target)
Results	•No difference in mortality •Trend toward more cardiac arrhythmias in high-target group •Patients ≥ 75 years old with low-MAP target had reduced hospital mortality

Lamontagne F, et al. *Intensive Care Med.* 2016; 42:542-550.

Norepinephrine vs. Dopamine

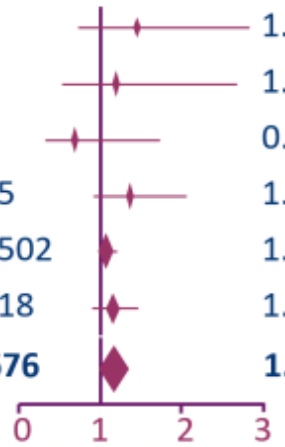


De Backer D, et al. *N Engl J Med.* 2010;362:779-789.

Norepinephrine vs. Dopamine

NE vs. DA in Septic Shock Meta-Analysis

Study	DA n/N	NE n/N	28-Day Mortality RR (95% CI)
Martin	10/16	7/16	1.43 (0.73-2.80)
Marik	6/10	5/10	1.20 (0.54-2.67)
Ruokonen	3/5	4/5	0.75 (0.32-1.74)
Mathur	19/25	14/25	1.36 (0.90-2.05)
De Backer	291/542	249/502	1.08 (0.98-1.19)
Patel	67/134	51/118	1.16 (0.89-1.51)
Overall	**396/732**	**330/676**	**1.12 (1.01-1.20)**

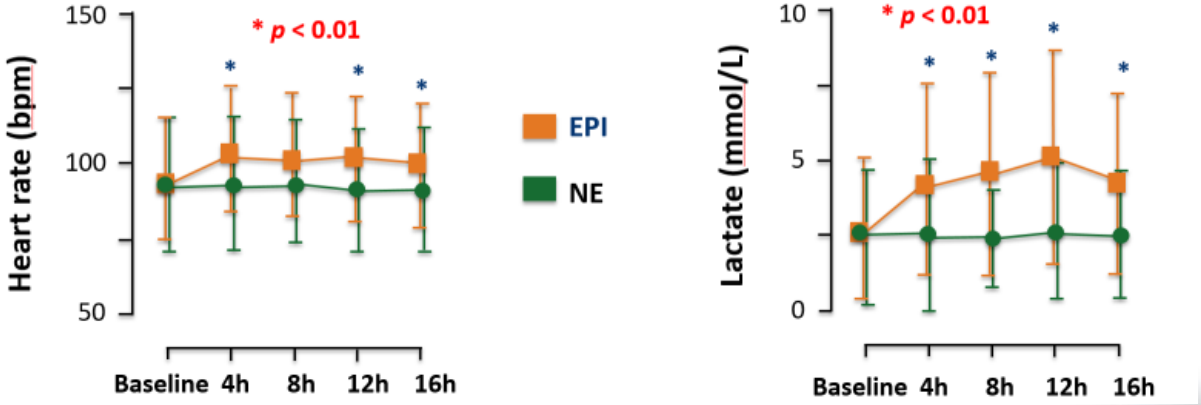


Overall effect p = 0.035
Heterogeneity p = 0.77, I^2 = 0%

De Backer D, et al. *Crit Care Med.* 2012;40:725-730.

Norepinephrine vs. Epinephrine

Variable	EPI	NE	p value
Time to MAP goal, median	35.1	40	0.26
Vasopressor-free days	26	25.4	0.31
28 day mortality, no (%)	31 (22.5)	36 (26.1)	0.48
Study drug discontinued, no (%)	18 (12.9)	4 (2.8)	0.002



Myburgh JA, et al. *Intensive Care Med*. 2008; 34:2226-2234. (adapted)

Vasopressin in Septic Shock

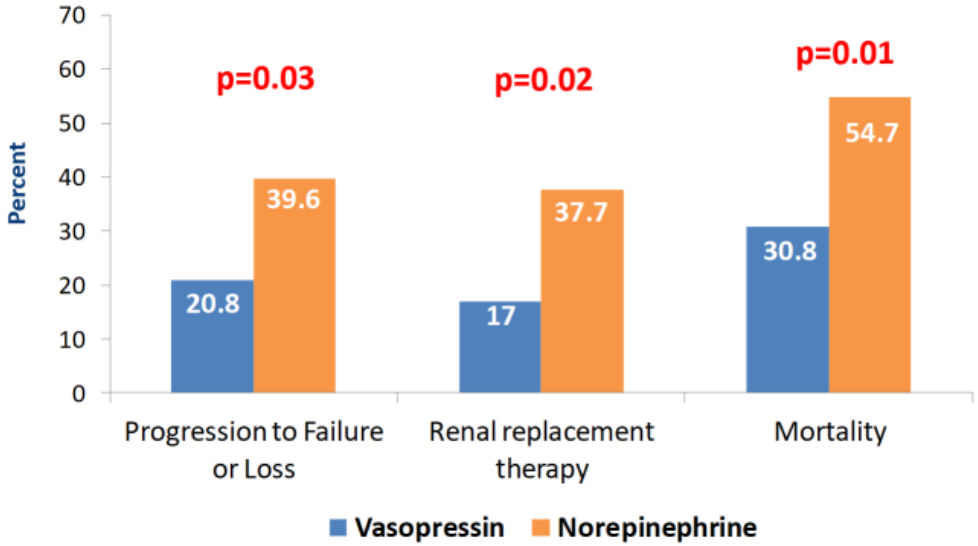
- Low fixed-dose vasopressin infusion (0.01-0.04 units /min) in septic shock:
  - Restores depleted physiologic levels
    - 0.04 units/min ~150-290 pmol/L
  - Spares high dose catecholamine
  - ↑ MAP
  - ↑ SVR
  - ↑ Urine output

Hollenberg SM. *Crit Care Clin.* 2009; 25:781–802.
Szumita PM, et al. *Am J Health Syst Pharm*. 2005; 62(18):1931-1936.

VASST

Patients	• Adult ICU patients with septic shock receiving norepinephrine
Methods	• Norepinephrine 5-15 mcg/min vs. Norepinephrine + vasopressin 0.01-0.03 units/min
Results	• 28-day mortality: vasopressin 35.4% v. norepinephrine 39.3% p=0.26 • Vasopressin group had a lower heart rate(p<0.001) • Vasopressin group had reduced norepinephrine use (p<0.001) • Patients with less severe shock had lower mortality with vasopressin use

Time to VP	NE mortality	VP mortality
< 12 hours	40.5%	33.2%
> 12 hours	37.5%	37.7%



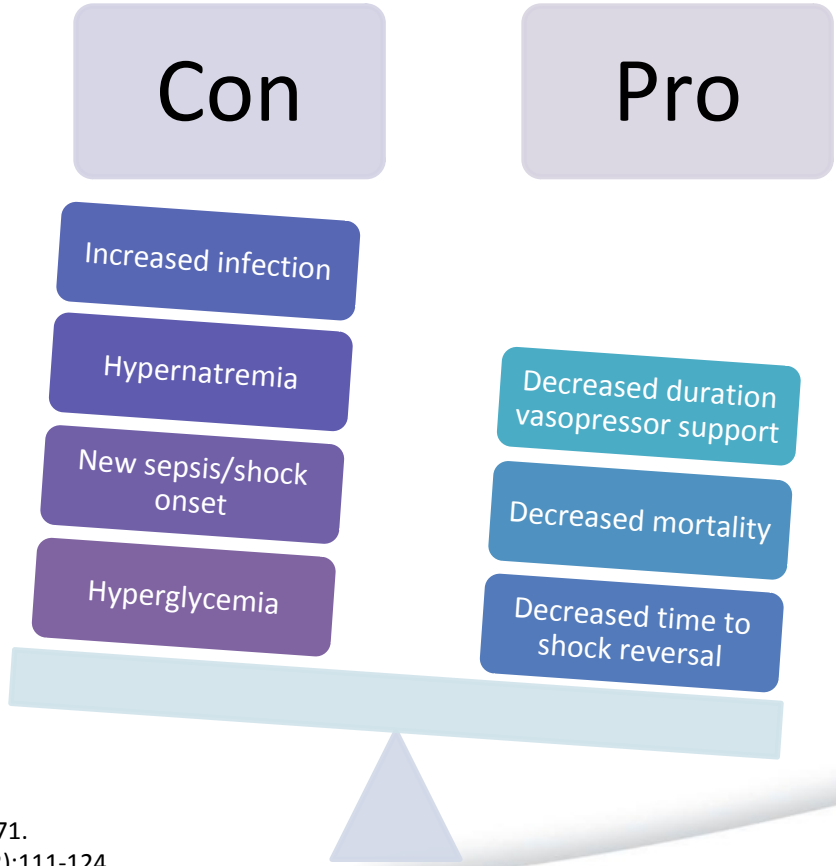
Russell JA, et al. *N Engl J Med.* 2008; 358:877-887.
Russell JA. *Crit Care*. 2011; 15:226-245.
Gordon AC, et al. *Intensive Care Med*. 2010; 36:83-91.

SSC Guidelines
Corticosteroid Therapy

- Weak Recommendation
  - IV hydrocortisone 200 mg/day if adequate fluid resuscitation and vasopressors do not restore hemodynamic stability

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377.

Corticosteroid Controversy



Annane D, et al. *JAMA*. 2002; 288(7):862-871.
Sprung CL, et al. *N Engl J Med*. 2008; 358 (2):111-124.

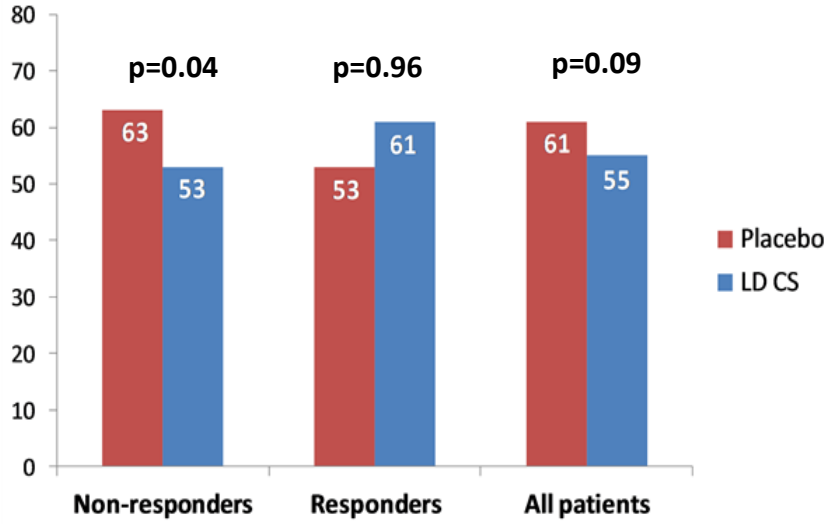
Days Until Shock Reversal

	Annane 2002			CORTICUS 2008		
	Placebo	LD CS	p value	Placebo	LD CS	p value
Non-responders	10	7	0.001	6.0	3.9	0.06
Responders	7	9	0.49	5.8	2.8	< 0.001
All patients	9	7	0.01	5.8	3.3	< 0.001

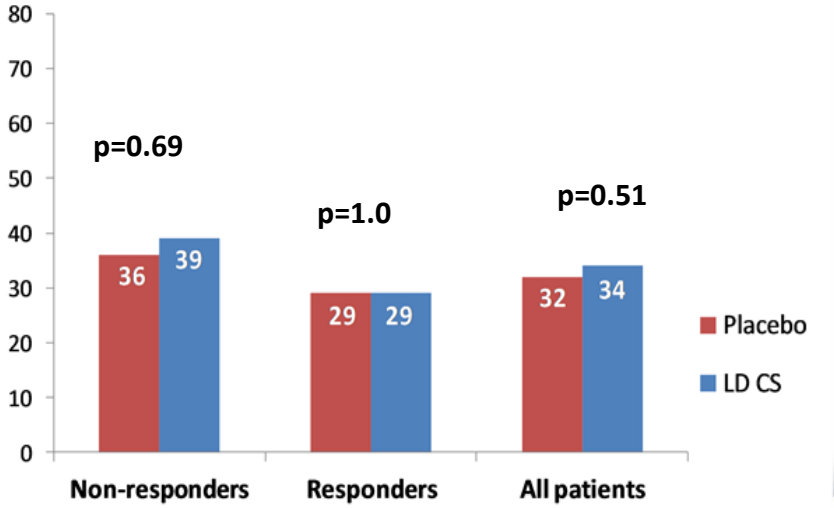
Annane D, et al. *JAMA*. 2002; 288:862-871.
Sprung CL, et al. *N Engl J Med*. 2008; 358:111-124.

Mortality

Annane 2002



CORTICUS 2008



Annane D, et al. *JAMA*. 2002; 288:862-871.
Sprung CL, et al. *N Engl J Med*. 2008; 358:111-124.

Corticosteroid Controversy

Annane 2002

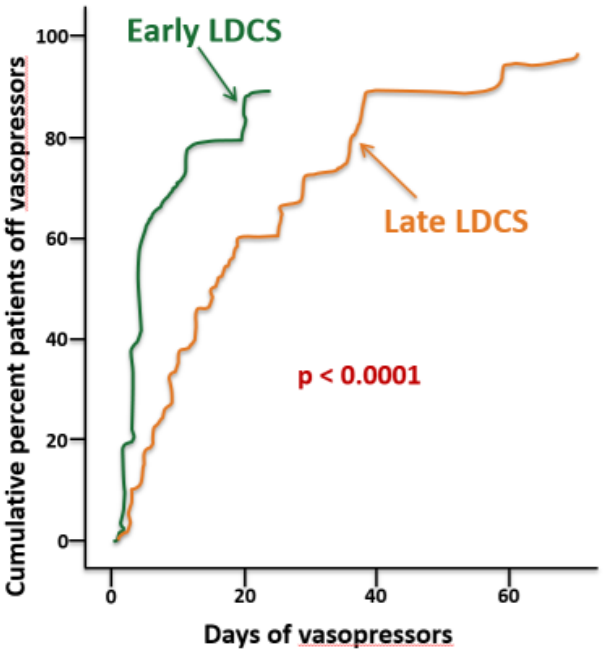
- SAPS II ~ 60
- Placebo mortality 61%
- Enrolled w/in 8hr
  - CS w/in 4hr pressor initiation
- MAP 55 mmHg
- Hydrocort + fludrocort x 7d
- 60% medical patients
- 77% non-responders
- Appropriate antibiotics
  - > 90% patients
  - Time to AA ~ 6 hours

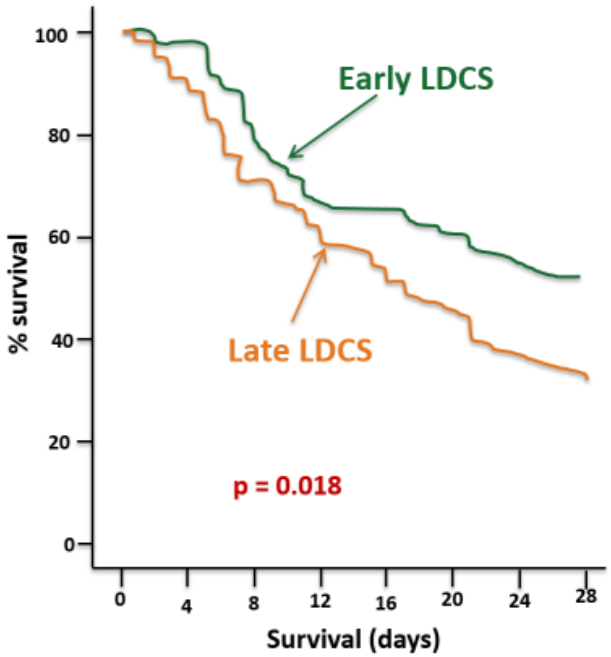
CORTICUS 2008

- SAPS II 48
- Placebo mortality 32%
- Enrolled w/in 72hr
  - CS w/in ?? pressor initiation
- SBP 94 mm Hg
- Hydrocort x 11d (taper)
- 35% medical patients
- 46.7% non-responders
- Appropriate antibiotics
  - ?

Annane D, et al. *JAMA*. 2002; 288:862-871.
Sprung CL, et al. *N Engl J Med*. 2008; 358:111-124.

Early Corticosteroids in Septic Shock





Katsenos CS, et al. *Crit Care Med*. 2014; 42:1651-1657. (adapted)

HYPRESS Trial

Patients	• Adult patients with severe sepsis, but not in shock
Methods	• Continuous infusion hydrocortisone 200 mg x 5 days followed by dose tapering until day 11 vs. Placebo
Results	• Development of septic shock within 14 days: Hydrocortisone 21.2% vs. placebo 22.9%, P=0.70 • No differences in time to septic shock or mortality • Hydrocortisone group had more secondary infections, weaning failure, muscle weakness, and hypernatremia (NS) • Significantly greater hyperglycemia with hydrocortisone (p=0.009)

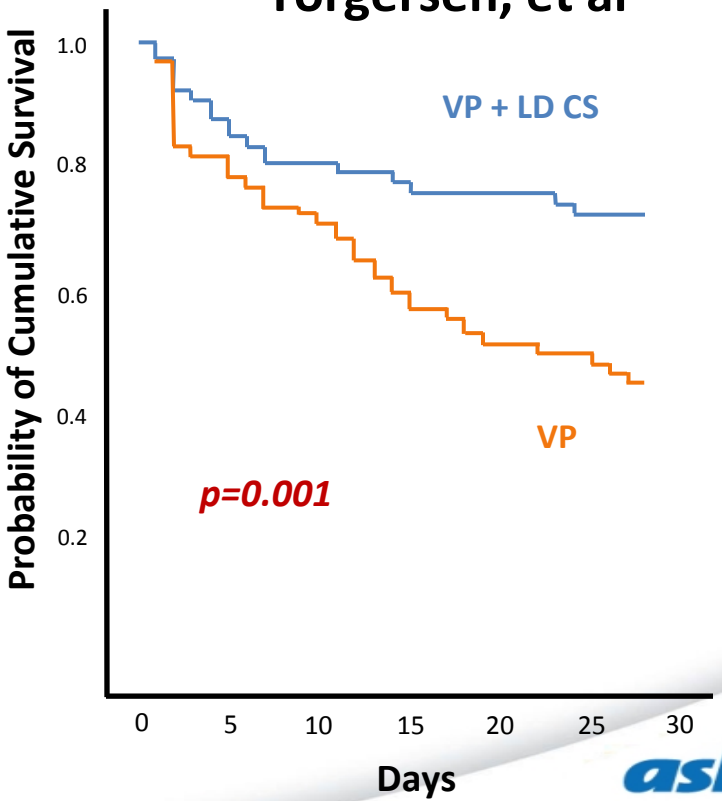
Keh D, et al. *JAMA*. 2016; 316:1775-1785.

Vasopressin and Corticosteroids

Bauer, et al

- Time from pressor initiation to first CS dose = 22.2 hours
- Median time to withdrawal of vasopressor support (p = 0.09)
  - CS = 65 hours
  - No CS = 20 hours
- Patients alive w/o vasopressors at day 7 (p = 0.02)
  - CS = 80.9%
  - No CS = 47.6%
- CS independently associated with survival w/o vasopressors at day 7

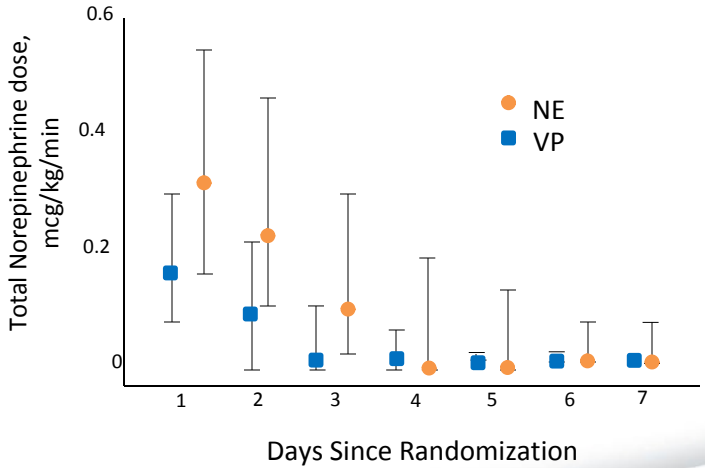
Torgersen, et al



Bauer SR, et al. *J Crit Care*. 2008; 23:500-506.
Torgersen C, et al. *Intensive Care Med*. 2011; 37(9):1432-1437. (adapted)

VANISH

Patients	• Adult ICU patients with septic shock, within 6 hours of shock onset
Methods	• Vasopressin + Hydrocortisone vs. Vasopressin + Placebo vs. Norepinephrine + Hydrocortisone vs. Norepinephrine + Placebo
Results	• 28-day survivors who never developed kidney failure: Vasopressin 57.0% vs. Norepinephrine 59.2% (difference -2.3%, 95% CI -13.0% to 8.5%) • No difference in mortality or adverse events • Less renal replacement therapy in vasopressin group (25.4% vs. 35.3%, 95% CI -19.3 to -0.6)



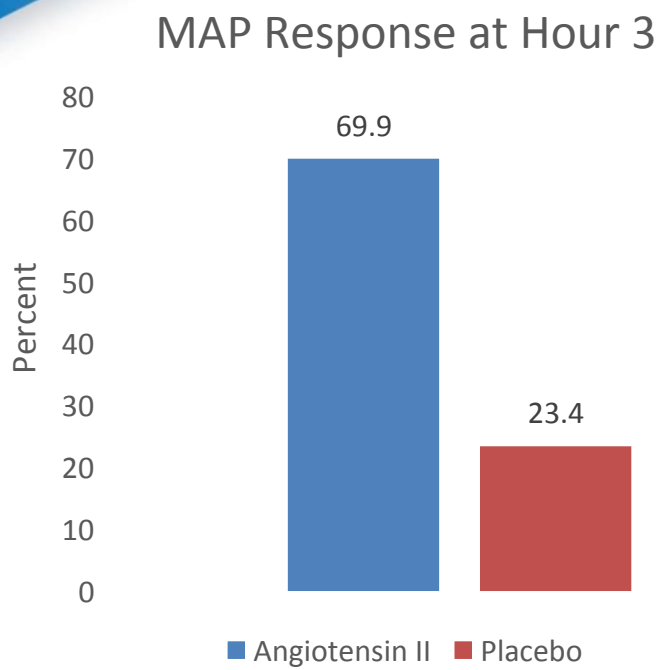
Gordon AC, et al. *JAMA*. 2016; 316:509-518. (adapted)

Short-Term Hemodynamic Effects of Hydrocortisone/Vasopressin

Patients	• **Adult patients with septic shock (n=300)**
Methods	• Retrospective cohort study of patients receiving AVP 0.04 units/min, HCT 200-300 mg/day, or AVP/HCT combination • "Response" defined as ≥ 50% reduction of NE dose by 4 hours (no Δ in MAP) • Reassessed at 12 and 24 hours
Results	• Higher response rate at 4 hours in concomitant AVP/HCT (88.5%) vs. HCT (62.3%) or VP (72.9%) monotherapy (p=0.0005) • Response rate significantly higher at 24 hours in concomitant group (p=0.032) and trend towards significance at 12 hours (0.052) • Significantly higher rate of NE in non-responders at all time intervals • Responders were more likely to be in AVP/HCT group • Responders had higher SOFA scores, were older, and were more likely to be on > 15 mcg/min of NE at baseline

Buckley MS, et al. *J Crit Care.* 2017; 42:6-11.

Angiotensin II – ATHOS 3

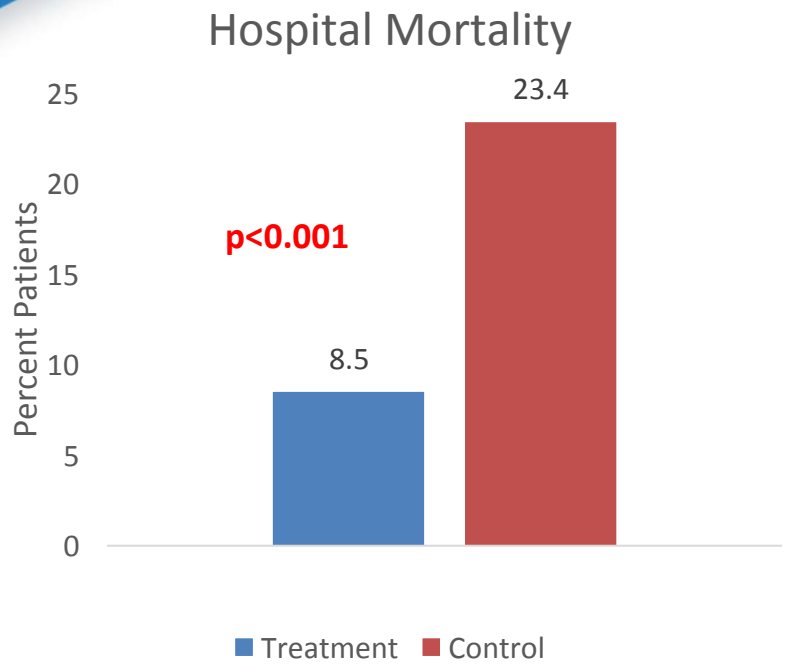


Endpoint	Angiotensin II	Placebo	P value
Δ CV SOFA at 48h$^{\alpha}$	-1.75 ± 1.77	-1.28 ± 1.65	0.01
Δ total SOFA at 48h$^{\alpha}$	1.05 ± 5.50	1.04 ± 5.34	0.49
Δ NE-equiv dose at 3h$^{\alpha}$	-0.03 ± 0.10	0.03 ± 0.23	<0.001
All cause mortality day 7$^{\beta}$	47 (29)	55 (35)	0.22
All cause mortality day 28$^{\beta}$	75 (46)	85 (54)	0.12

α mean ± SD
β No. (%)

Khanna A, et al. *N Engl J Med*. 2017; 377:419-430.

Vitamin C + Hydrocortisone + Thiamine



Endpoint	Treatment	Control	P value
ICU LOS, d[α]	4 (3-5)	4 (4-10)	NS
Duration vasopressors[β]	18.3 ± 9.8	54.9 ± 28.4	<0.001
RRT for AKI (%)	10	33	0.02
Δ SOFA, 72h[β]	4.8 ± 2.4	0.9 ± 2.7	<0.001
Procalcitonin clearance, median % and IQR, 72h	86.4 (80.1 to 90.8)	33.9 (-62.4 to 64.3)	<0.001

α median (IQR)
β mean ± SD

Marik PE, et al. *Chest*. 2017; 151:1229-1238.

Key Takeaways

- Key Takeaway #1
  - Understand both international guidelines and CMS SEP-1 requirements, to develop a local sepsis care path which follows best practices
- Key Takeaway #2
  - Continually reassess patients using dynamic markers, if possible, and patient-specific variables to individualize management based on response
- Key Takeaway #3
  - Septic shock is associated with high mortality. Management strategies and treatment options are still evolving.