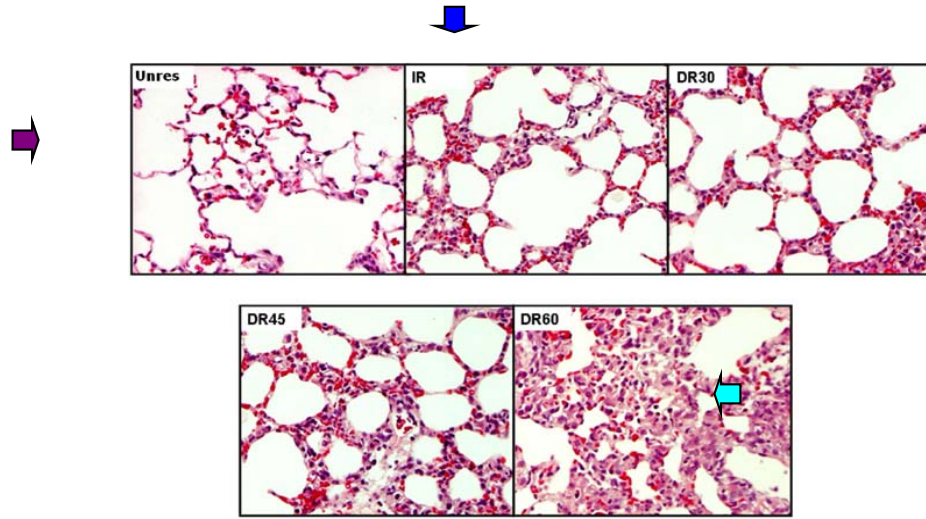


Management of the Septic Patient: New Definitions & New Guidelines



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GOALS of the LECTURE – TO REVIEW

- 1. New Definitions of Sepsis and Shock**
2. New Surviving Sepsis Guidelines 2016

45M with fever, cough, and dyspnea for 3 days. T 40.0 C, BP 110/70, HR 100, RR 26. Looks acutely ill, lethargic and disoriented. Rales at the R lung base. Urine output 5/hr. WBC $15 \times 10^9/L$, Hb 8.2 g/dL, Platelets $180 \times 10^9/L$. Na 138, K 4.9, Cl 105, HCO₃ 18, Cr 2.0 Lactate 6 mEq/L. Urine analysis is unremarkable. A sputum, urine, and blood cultures are sent. Chest film - right lower lobe infiltrate.

This patient has:

- a) Bacteremia
- b) Sepsis
- c) Severe Sepsis
- d) Septic Shock

SEPSIS-3 Definitions. Singer. JAMA 2016; 315: 801-10.



OLD DEFINITION

SIRS

WBC; RR; T; HR

Severe Sepsis

Sepsis +
Organ Failure
Or Lactate

MR 20%

Sepsis

SIRS + Infection

Septic Shock

SBP < 90

MR 16%

MR 46%

SEPSIS-3 Definitions. Singer. JAMA 2016; 315: 801-10.



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NEW DEFINITION

Sepsis

Infection
Dysregulated Host Response
Organ Dysfunction

MR 10%

SOFA ≥ 2

Septic Shock

Vasopressors &
Lactate > 2

MR 40%

SEPSIS-3 Definitions. Singer. JAMA 2016; 315: 801-10.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
Pao ₂ /Fio ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
MAP ≥70 mm Hg		MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

SOFA ≥2
 PF <300
 PLT <100
 Bili >2
 Pressors
 GCS ≤12
 Cr >2

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qSOFA ≥ 2

Delta MS

RR ≥ 22

SBP ≤ 100

SOFA ≥ 2

PF < 300

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Pressors

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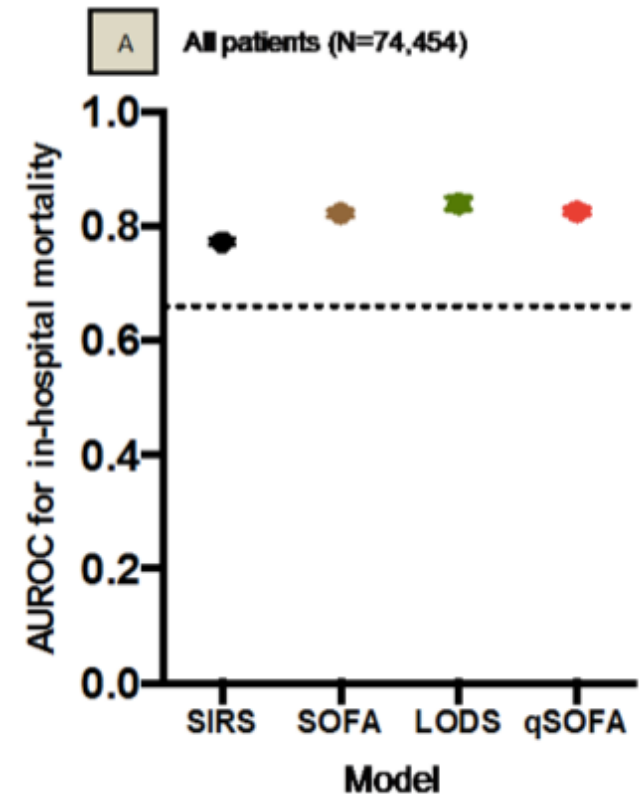
SBP ≤ 100

SOFA ≥ 2

CONTROVERSIES?

Worth the Complexity?

Implications for LMIC?



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This patient has:

- a) Bacteremia
- ☒ b) Sepsis **New Sepsis 3 Definition**
- c) Severe Sepsis **Old Definition**
- d) Septic Shock

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2. **New Surviving Sepsis Guidelines 2016**

45M with fever, cough, and dyspnea for 3 days. T 40.0 C, BP 110/70, HR 100, RR 26. Looks acutely ill, lethargic and disoriented. Rales at the R lung base. Urine output 5/hr. WBC $15 \times 10^9/L$, Hb 8.2 g/dL, Platelets $180 \times 10^9/L$. Na 138, K 4.9, Cl 105, HCO₃ 18, Cr 2.0 Lactate 6 mEq/L. Urine analysis is unremarkable. A sputum, urine, and blood cultures are sent. Chest film - right lower lobe infiltrate.

BP is now 85/30. Which of the following will improve survival?

- a) Albumin
- b) Blood Transfusion to achieve Hb >10
- c) Choice of Norepinephrine over Dopamine
- d) Fluids and Vasopressors to Target MAP >80 vs. >65.
- e) Early goal directed therapy to achieve MAP>65, urine > 0.5 ml/kg/h, CVP > 8 and SVO₂ Sat > 70%.
- f) None of the Above

SURVIVING SEPSIS GUIDELINES

OVERALL –
93 Recommendations

EARLY MANAGEMENT -
43 Recommendations

“STRONG” - 11
“BEST PRACTICE” - 13

Policy or
Quality Indicators

SURVIVING SEPSIS GUIDELINES

OVERALL –
93 Recommendations

EARLY MANAGEMENT -
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Policy or
Quality Indicators

7 SUMMARY Points

Immediate Resuscitation

Choice of Fluids

Hb Goal

Choice of Vasopressors

MAP Goal




Timing of Antibiotics

Source Identification & Control

Immediate Resuscitation (BPS)

Lee. Ann Emerg Med 2007; 49: 37-44.

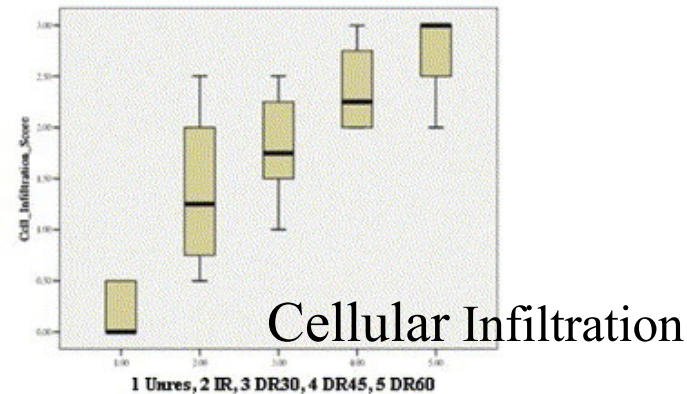
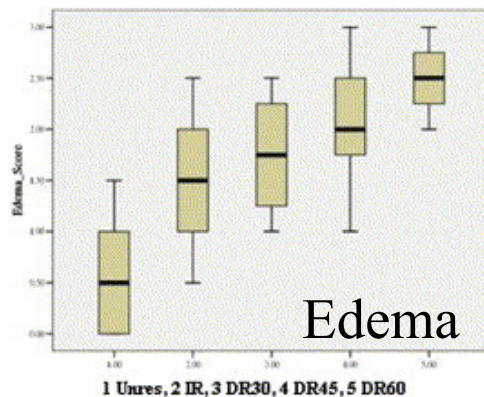
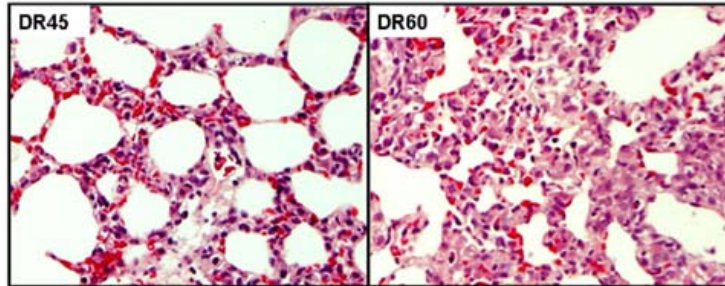
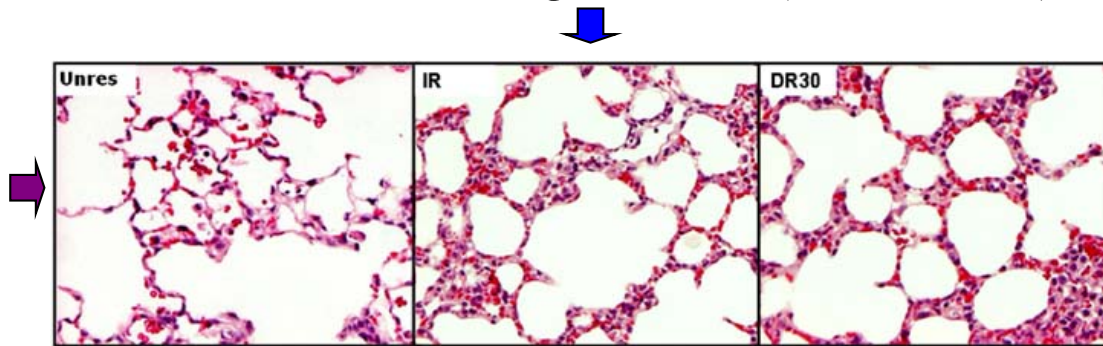
Rat model of hemorrhagic shock (30 minutes).

Immediate 
Delay 60 
No Resuscitation 

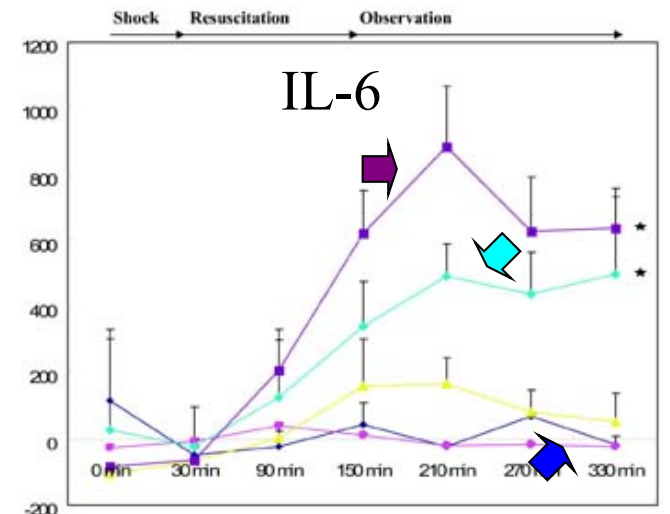
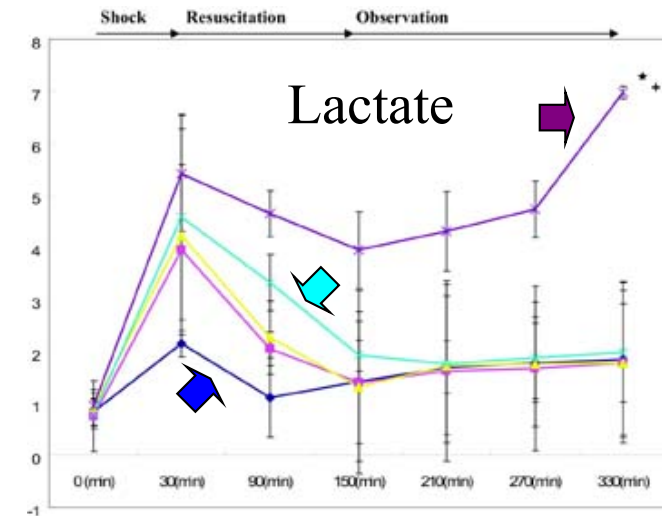
Immediate Resuscitation (BPS)

Lee. Ann Emerg Med 2007; 49: 37-44.

Rat model of hemorrhagic shock (30 minutes).



Immediate
Delay 60
No Resuscitation



Choice of Fluids? (Strong)

	WISEP Trial NEJM 2008	6S Trial NEJM 2012	CHEST Trial NEJM 2012
Population	537 S. Sepsis ICU Patients	798 S. Sepsis ICU Patients	7000 needing resuscitation
Intervention	10% Pentastarch	6% Hetastarch	6% Hetastarch
Comparison	LR	R Acetate	NS
Outcome	Death @ 28d	Death @ 90d or Dialysis	Death @ 90d
Risk of Bias	High-Allocation	Low	Low

Mortality
Benefit?

Other
Findings?

Choice of Fluids? (Strong)

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Mortality Benefit?

No 27% v. 24%
P = 0.48

No 18% v. 17%
P = 0.26

MORE Death or RRT
51% v. 43%, P = 0.03

Other Findings?

MORE RRT -
31% v. 19%, P =
0.001

MORE RRT - 7.0%
v. 5.8%, P = 0.04

MORE RRT -
22% v. 16%, P =
0.04

Choice of Fluids? (Strong)

	SAFE Trial NEJM 2004	ALBIOS Trial NEJM 2014.
Population	6997 ICU Patients	1818 S. Sepsis ICU Patients
Intervention	4% Albumin	20% Albumin for Target Albumin >3
Comparison	NS	Crystalloids
Outcome	Death @ 28d	Death @ 28d
Risk of Bias	Intermediate-Registry	Low

Mortality
Benefit?

New Organ
Failure?

Choice of Fluids? (Strong)

	SAFE Trial NEJM 2004	ALBIOS Trial NEJM 2014.
Population	6997 ICU Patients	1818 S. Sepsis ICU Patients
Intervention	4% Albumin	20% Albumin for Target Albumin >3
Comparison	NS	Crystalloids
Outcome	Death @ 28d	Death @ 28d
Risk of Bias	Intermediate-Registry	Low

Mortality Benefit?

No 21% v. 21%
P = 0.87

No 32% v. 32%
P = 0.94

New Organ Failure?

No 53% v. 53%
P = 0.85

No 44.5% v. 45.5%
P = 0.99

Hb Target (Strong)

	Villeneuve NEJM 2013	TRISS Trial NEJM 2014
Population	921 Severe UGIB Patients	998 Septic Shock Patients
Intervention	Hb Goal >9.0	Hb Goal >9.0
Comparison	Hb Goal >7.0	Hb Goal >7.0
Outcome	Death @ 45d	Death @ 90d
Risk of Bias	Low – Single Center	Low

Mortality
Benefit?

Rebleeding
Risk?

Hb Target (Strong)

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Population	921 Severe UGIB Patients	998 Septic Shock Patients
Intervention	Hb Goal >9.0	Hb Goal >9.0
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Outcome	Death @ 45d	Death @ 90d
Risk of Bias	Low – Single Center	Low

Mortality Benefit?

More Deaths with Hb >9.0
9% v. 5%, P = 0.02

No 45% v. 43%
P = 0.44

Rebleeding Risk?

More Rebleeding with Hb >9.0
16% v. 10% P = 0.01

Choice of Vasopressors (Strong)

	SOAP II Study NEJM 2010	VASST Trial NEJM 2008.
Population	1679 Patients with Shock	802 Sepsis Patients on Norepinephrine
Intervention	Norepinephrine	Switch to Vasopressin
Comparison	Dopamine	Continue with NE
Outcome	Death @ 28d	Death @ 28d
Risk of Bias	Low	Low

Mortality
Benefit?

Other
Findings?

Choice of Vasopressors (Strong)

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Intervention	Norepinephrine	Switch to Vasopressin
Comparison	Dopamine	Continue with NE
Outcome	Death @ 28d	Death @ 28d
Risk of Bias	Low	Low

Mortality Benefit?

No 48% v. 52%, $P = 0.10$

No 35% v. 39%
 $P = 0.26$

Other Findings?

More arrhythmias with DOPA
24% v. 12%, $P < 0.001$

Serious adverse events
10% v. 10%, $P = 1.00$

MAP Goal? (Strong)

	SEPSISPAM Trial NEJM 2014
Population	798 Septic Shock Patients
Intervention	MAP Target 80-85
Comparison	MAP Target 65-70
Outcome	Death @ 28d
Risk of Bias	Low

Mortality
Benefit?

MAP Goal? (Strong)

	SEPSISPAM Trial NEJM 2014
Population	798 Septic Shock Patients
Intervention	MAP Target 80-85
Comparison	MAP Target 65-70
Outcome	Death @ 28d
Risk of Bias	Low

Mortality
Benefit?

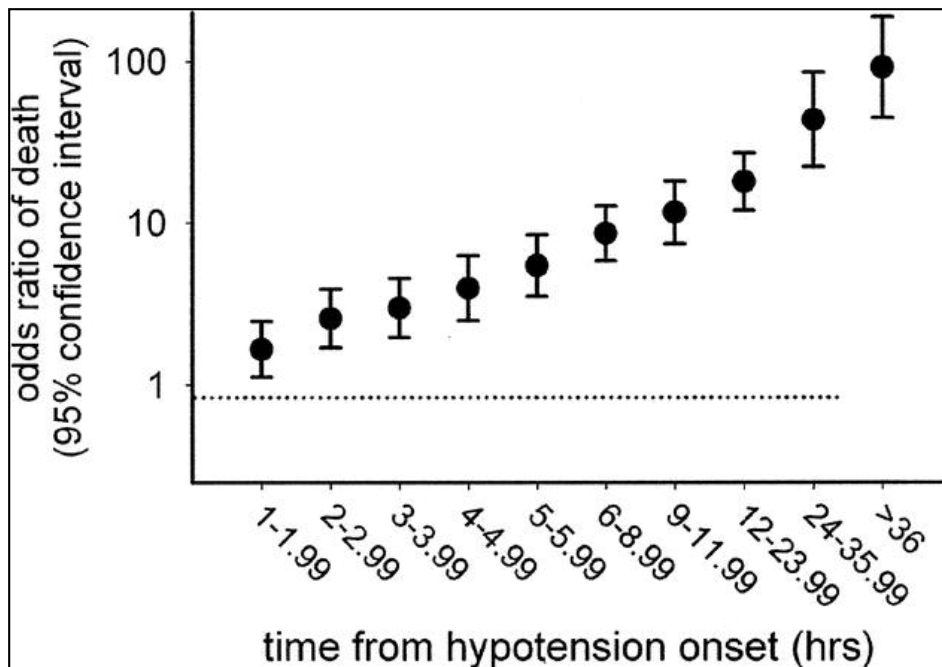
No 37% v. 34%, $P = 0.57$

Timing of Antibiotics? (Strong)

Kumar. CCM 2006; 34: 1589-96.

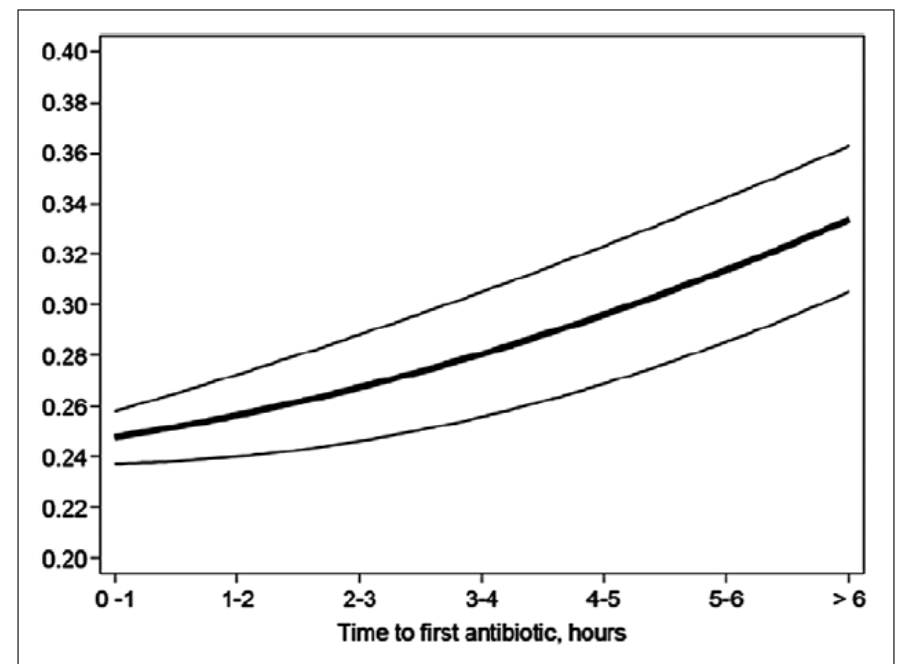
Retrospective analysis 2731 adult septic shock patients.

Each Hour of Delay? 8% Increase in Mortality



Ferrer. CCM 2014; 42: 1749-55.

Retrospective analysis 17990 adult severe sepsis and septic shock patients.



Source Identification & Control (Strong)

Common Sources
Of Septic Shock

Lungs
Urinary Tract
Abdomen
(Central Venous Catheters)

Uncommon Sources
Of Septic Shock

Cellulitis
Osteomyelitis
Decubitus ulcer
Pneumocystis carinii

Sources That Typically
Need Further Control
(In Addition to Antibiotics)

Parapneumonic effusions
Necrotizing fasciitis
Abscesses
Perforated viscus
Infected catheters & devices

Protocol-Based Resuscitation?

	Rivers. NEJM 2001
Population	263 Severe Sepsis Patients
Intervention	Protocol to Achieve within 6 Hours (MAP >65, CVP >8–12, UO >0.5, SVO ₂ >70%.)
Comparison	Usual Care to Achieve within 6 Hours (MAP >65, CVP >8–12, UO >0.5.)
Outcome	Hospital Mortality
Risk of Bias	

Mortality
Benefit?

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Comparison	Usual Care to Achieve within 6 Hours (MAP >65, CVP >8–12, UO >0.5.)
Outcome	Hospital Mortality
Risk of Bias	High Risk of Bias – Not Registration, Single Center, Conflict of Interest, Unequal Treatment

Mortality
Benefit?

Yes 46% v. 30%, P = 0.01

Protocol-Based Resuscitation?

	Process Trial NEJM 2014	ARISE Trial NEJM 2014	Promise Trial NEJM 2015
Population	1351 S. Sepsis Patients @ US Academic Hospitals w/o Protocols	1600 Early S. Sepsis ER Patients Mostly in Oceania	1260 S. Sepsis Patients @ UK Hospitals Not Using SVCSat
Intervention	CVP >8, MAP >65, SVSat >70%, HCT >30%		
Comparison	Usual Care	No Protocol	Usual Care
Outcome	Death @ 60d	Death @ 90d	Death @ 90d
Risk of Bias	Low	Low	Low

Mortality
Benefit?

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Outcome	Death @ 60d	Death @ 90d	Death @ 90d
Risk of Bias	Low	Low	Low

**Mortality
Benefit?**

No 21% v. 19%
P = 0.83

No 19% v. 19%
P = 0.90

No 30% v. 29%
P = 0.90

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- f) None of the Above

SUMMARY – Surviving Sepsis 2016 Guidelines

1. Resuscitation should be started **immediately**. (BPS)
2. IVF and/or vasopressors is generally indicated to achieve **MAP >65**. Higher MAP target does not improve clinical outcome. (Strong)
3. **Crystalloid** rather than colloid fluids should be initially used for resuscitation. (Strong)
4. **Hb target** should be **>7.0** g/dL. Higher Hb targets do not improve clinical outcome. (Strong)
5. Among dopamine, norepinephrine or vasopressin, there is no survival advantage with the use of one **vasopressor** over another. However, norepinephrine is preferred over dopamine because of fewer side effects than dopamine. (Strong)
6. Appropriate broad-spectrum IV antibiotics should be started as soon as possible. (Strong)
7. Source of the sepsis should be identified and controlled asap. (BPS)
8. Targeting arbitrary goals or adhering to any specific **protocols** (e.g. EGDT) do not offer any clinical advantages beyond usual care.

SUMMARY – Surviving Sepsis 2016 Guidelines

1. Resuscitation should be started **immediately**. (BPS)
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 4. **Hb target** outcome.
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- Resuscitate Early**
Give Antibiotics Early
Source Identify and Control Early
- Good News for LMIC?**
- and asap. (BPS)
protocols (e.g. EGDT) do not offer any clinical advantages beyond usual care.

