Management of sepsis
What to do what not to do?

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"Symposium about severe infections:
A multidisciplinary Approach"

COI Disclosures

Djillali Annane

No financial disclosure

Member of the Sepsis 3 Task Force

Member of the SSC panel for 2008; 2012 and 2016 updates

Step 1

- Recognizing sepsis

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

The Sepsis Definitions Task Force

Task Force Decisions

CONSENSUS

1. Beyond the remit of the task force to define infection
2. **Sepsis is not simply infection + two or more SIRS criteria**
3. The host response is of key importance
4. **Sepsis represents** bad infection where

   bad = infection leading to organ dysfunction
5. **"Severe sepsis" is not helpful and should be eliminated**

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening *organ dysfunction* caused by a dysregulated host response to infection

So … "sepsis" now = the old "severe sepsis"

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening organ dysfunction caused by a *dysregulated host response* to infection

As opposed to the
"regulated host response"
that characterizes the non-septic response to infection

The Definition of Septic Shock

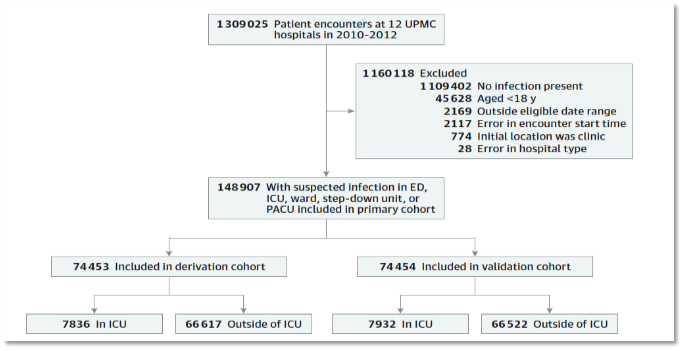
- What tangibly differentiates septic shock from sepsis ?
  - MORTALITY
    - Septic shock is "really bad" sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

The Need for Something Additional

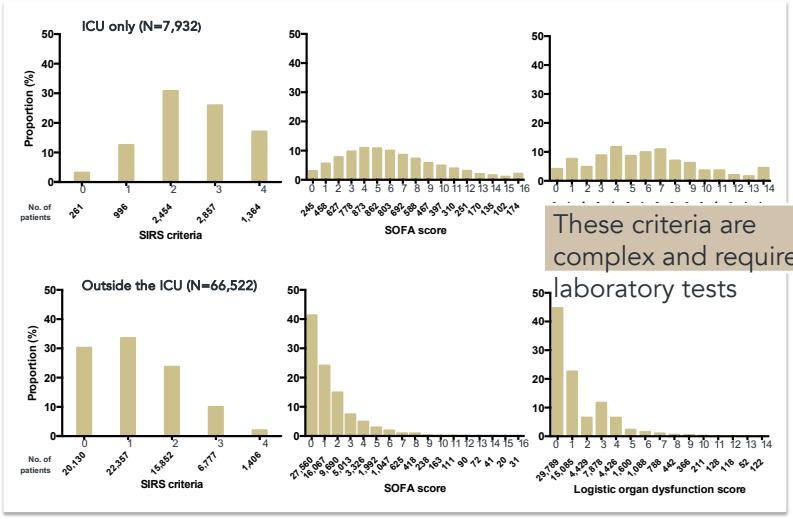
- Practitioners require something of value at the bedside
  - Preferably data-driven
- Clinical criteria
  - Existing
  - Newly derived and validated

What data source to use?



Characteristics	KPNC	VA	ALERTS	KCEMS
Years of cohort	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	20	130	1	14
Total No. of encounters	1 847 165	1 640 543	38 098	50 727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington

Distribution of existing criteria



These criteria are complex and require laboratory tests

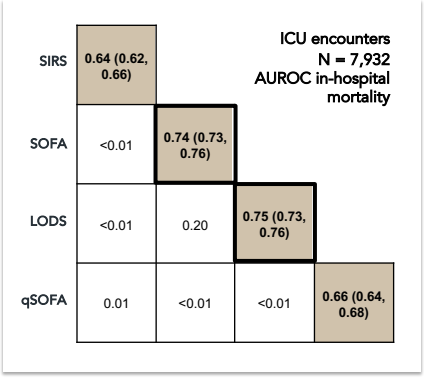
Developing new criteria

- Focus on timeliness, ease of use
- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality

qSOFA

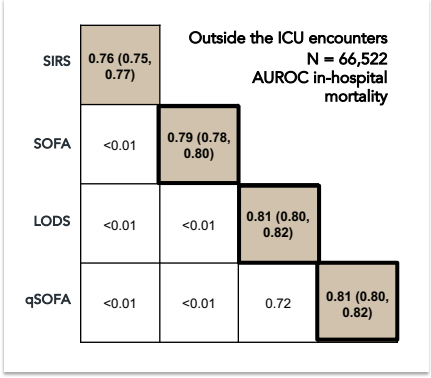
- Respiratory rate ≥ 22 bpm
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg

Assessment of Sepsis criteria



SOFA and LODS superior in the ICU

SEPSIS = INFECTION + SOFA ≥ 2



qSOFA similar to complex scores outside the ICU

At RISK for SEPSIS INFECTION + qSOFA≥2

SEPTIC SHOCK

- Definition

  Septic shock is defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

- Clinical criteria

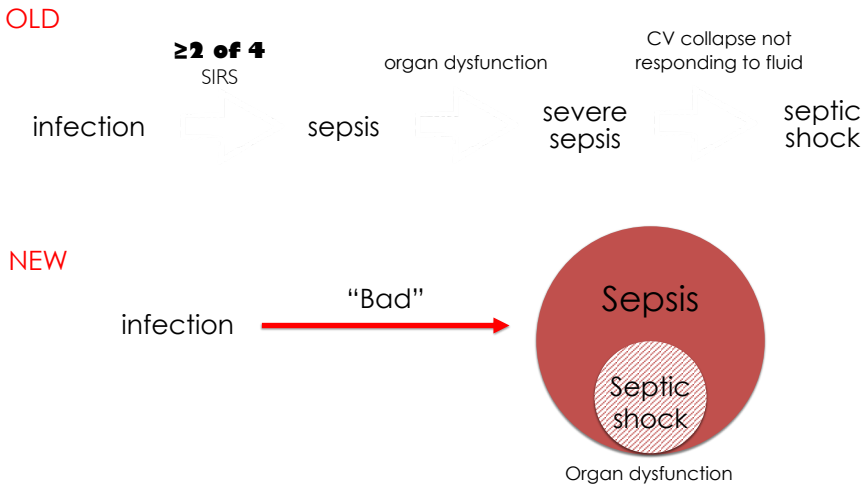
  Despite adequate fluid resuscitation, lactate >2 mmol/l and vasopressors needed to elevate MAP≥65 mmHg

Why hypotension AND hyperlactatemia for septic shock?

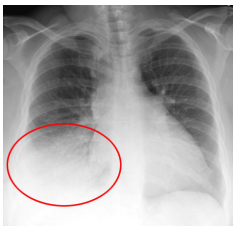
	hospital mortality (%)
hypotension + lactate >2	42.3
hypotension alone	30.1
lactate >2 alone	25.7
no hypotension and lactate <2	18.7

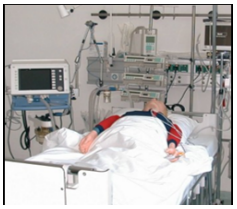
Shankar-Hari et al. JAMA 2016

Conceptual changes



Definition





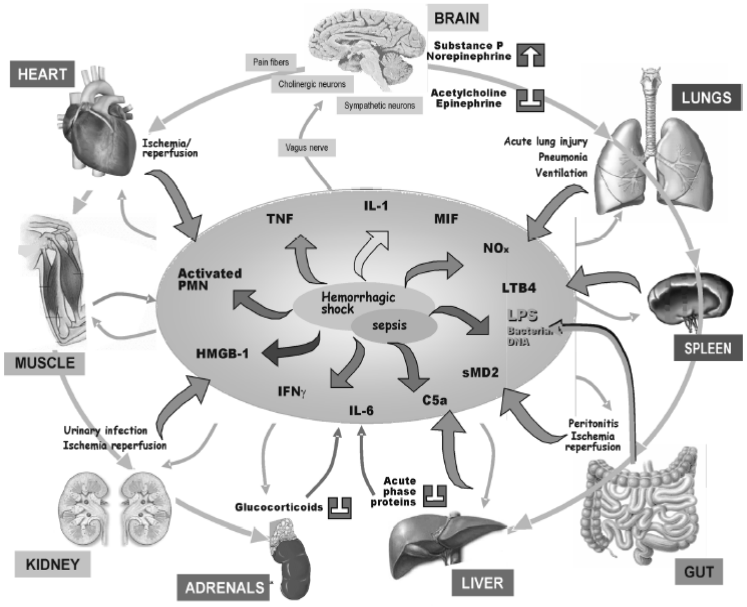
Infection

SOFA>2

LACTATE >2
VASOPRESSOR

- ***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

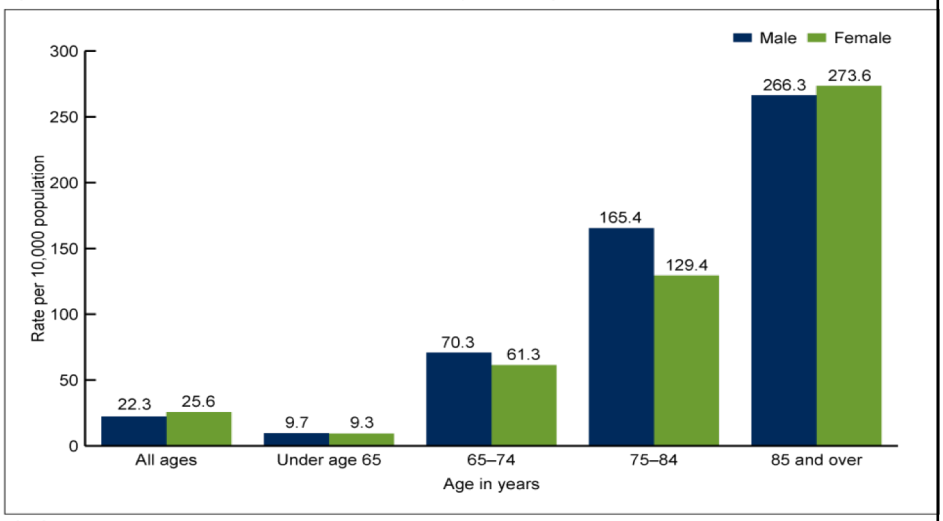
JAMA. 2016



Cavaillon JM & Annane D, JER 2007

Who is at risk?

Figure 2. Rates of hospitalization for septicemia or sepsis, by sex and age, 2008

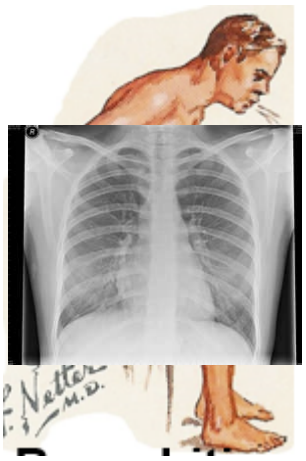


NOTES: Rates are significantly higher for males and females in each successive age group.
SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

NCHS Data Brief 2011

Patient Identification

ER / General wards



JAMA 2016

What are the bugs?

	Estimated frequency*
Gram-positive bacteria	30–50%
Meticillin-susceptible *S aureus*	14–24%
Meticillin-resistant *S aureus*	5–11%
Other *Staphylococcus* spp	1–3%
Streptococcus pneumoniae	9–12%
Other *Streptococcus* spp	6–11%
Enterococcus spp	3–13%
Anaerobes	1–2%
Other gram-positive bacteria	1–5%
Gram-negative bacteria	25–30%
E coli	9–27%
Pseudomonas aeruginosa	8–15%
Klebsiella pneumoniae	2–7%
Other *Enterobacter* spp	6–16%
Haemophilus influenzae	2–10%
Anaerobes	3–7%
Other gram-negative bacteria	3–12%
Fungus	
Candida albicans	1–3%
Other *Candida* spp	1–2%
Yeast	1%
Parasites	1–3%
Viruses	2–4%

*From published clinical trials[4,5,58] and epidemiological studies.[5,6]

***Table 1:* Main pathogens in septic shock**

Surviving Sepsis Campaign

ONE HOUR BUNDLE
We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials (BPS).

Annane, Lancet 2005

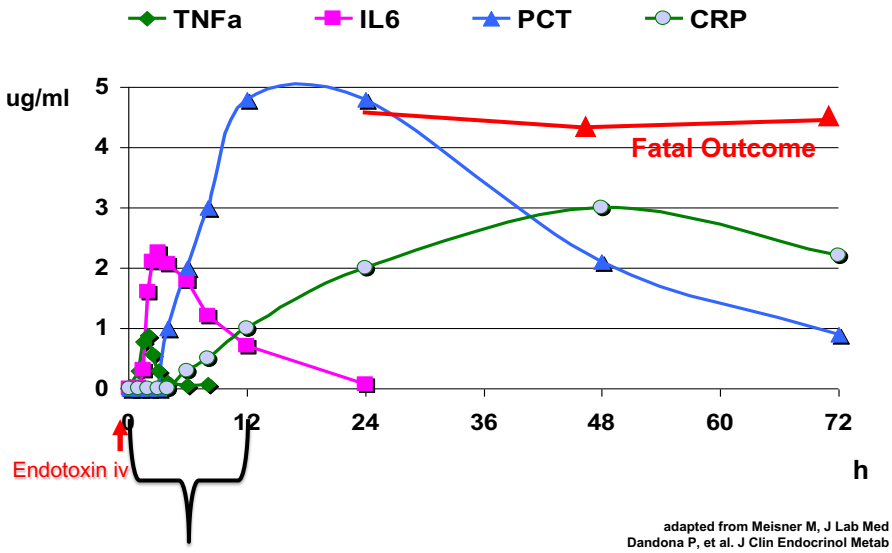
What are the sources of Sepsis

Table 4. Common sites of infection in patients with severe sepsis by sex and associated crude mortality rates (based on Mayr et al.)[37]

Site of infection	Frequency (%)		Mortality (%)	
	Male	Female	Male	Female
Respiratory	41.8	35.8	22.0	22.0
Bacteremia, site unspecified	21.0	20.0	33.5	34.9
Genitourinary	10.3	18.0	8.6	7.8
Abdominal	8.6	8.1	9.8	10.6
Device-related	1.2	1.0	9.5	9.5
Wound/soft tissue	9.0	7.5	9.4	11.7
Central nervous system	0.7	0.5	17.3	17.5
Endocarditis	0.9	0.5	23.8	28.1
Other/unspecified	6.7	8.6	7.6	6.5

Mayr, Virulence 2014

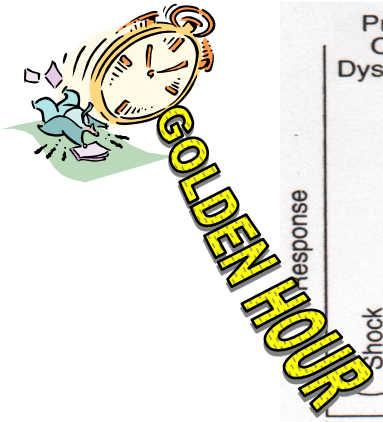
Kinetics of PCT upon Infection

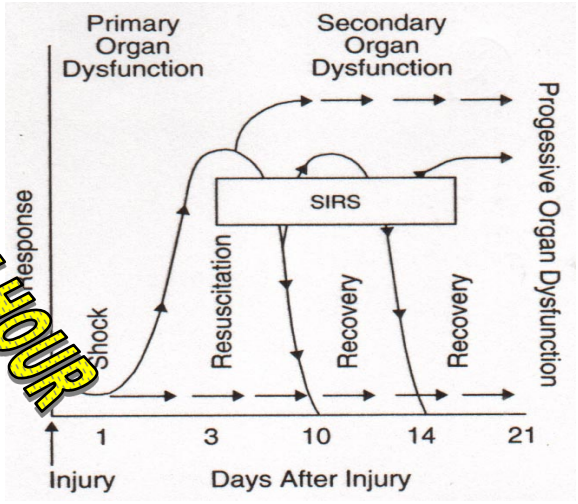


adapted from Meisner M, J Lab Med 1999
Dandona P, et al. J Clin Endocrinol Metab 1994
Harbarth S, AJRCCM 2001
Becker KL, J Clin Endocrinol Metab 2004

Step 1	• Recognizing sepsis
Step 2	• Start ATB

TIME IS IMPORTANT





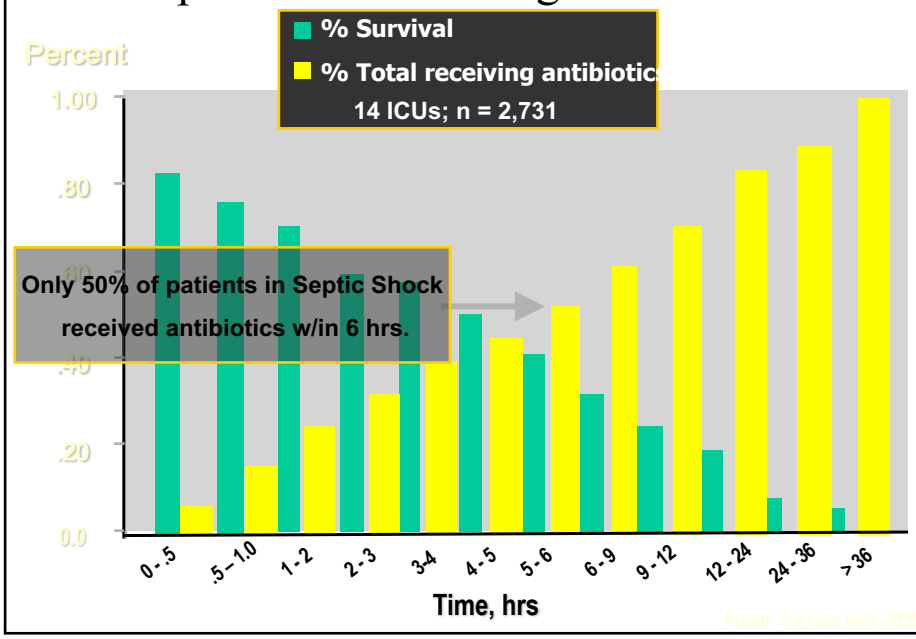
Surviving Sepsis Campaign guidelines 2018

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

Best Practice Statement

Control of Infection

Septic Shock: Timing of Antibiotics



Kumar, *Crit Care Med*, 2006

Don't Miss in the ER

- 'community' acquired ESB- Coli
- 'community' acquired MRSA
- Many factors innfluence the risk of MRB in patients admitted to the ER
  - Previous hospitalizations
  - Previous exposure to ATB
  - Long-care facilities

Monitoring antimicrobial drugs in ICU patients (B lactams, FQ)

n=240 (first monitoring)

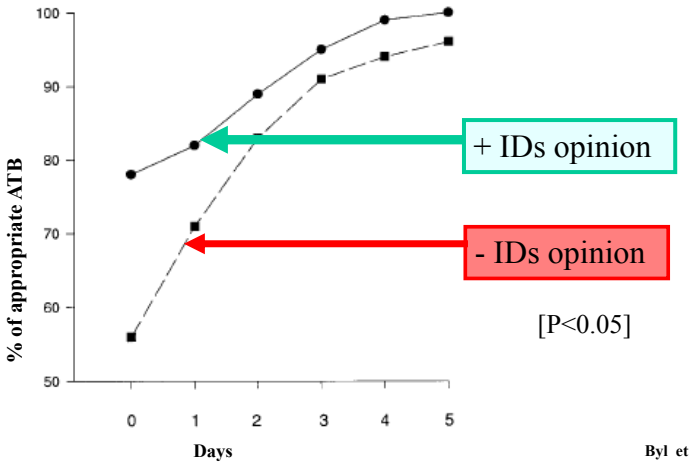
Retrospective study, St Joseph hospital, 5 years
Comparisons of the espected level (Pharmacology dpts) and observed levels

	Underdosed levels n=40 (16%)	Appropriate levels n=106 (42%)	Overdosed levels n=106 (42%)
Low dosage	7 (19.4%)	15 (14.8%)	4 (3.7%)
Standard dosage	24 (12.2%)	58 (57.4%)	77 (72.6%)
Elevated dosage	5 (12.5%)	28 (27.7%)	25 (23.6%)

Bouldouyre et al - Intens Care Med 2005; S223

Impact of ID expert's opinion

Bacteremia



[P<0.05]

Byl et al, *CID 1999, 29:60*

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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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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).**

De-escalation

Antibiotic Stewardship

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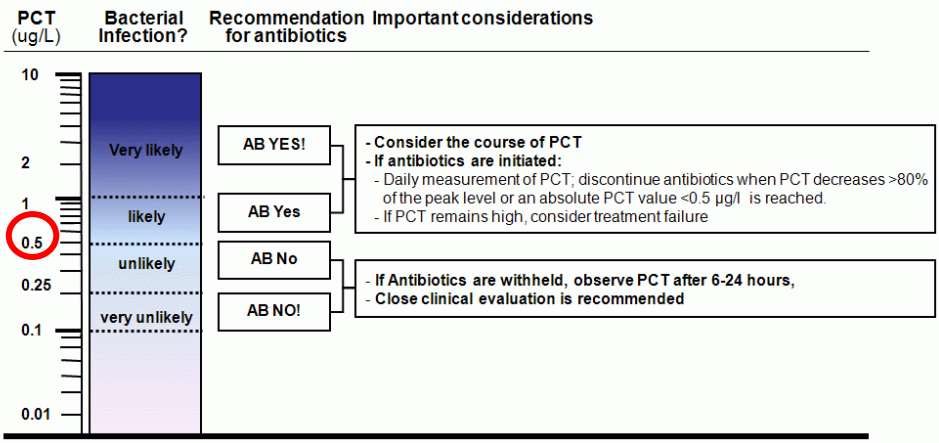
- **We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.**
  - **(BPS)**
- **We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated 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)**

ICU Patients with Sepsis



Schuetz P, CHEST, 2012

Reduced time on ATB

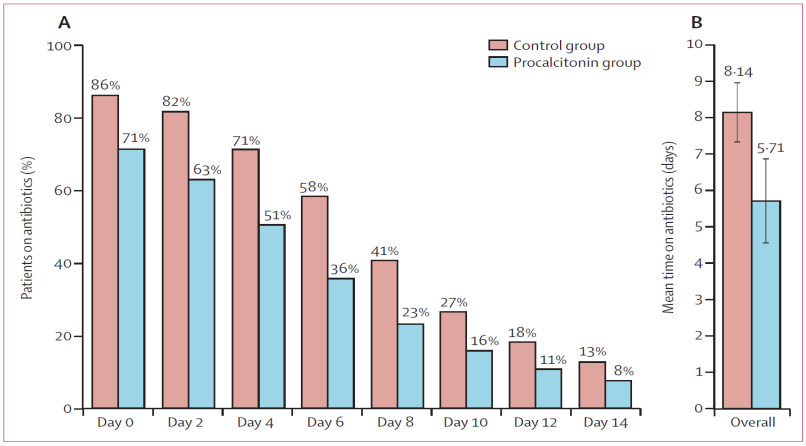


***Figure 3*: Antibiotic use**
(A) Proportions of patients on antibiotics. (B) Mean duration of antibiotic use.

Cochrane DBSR 2018; Lancet Infec Dis 2018

Step 1

- Recognizing sepsis

Step 2

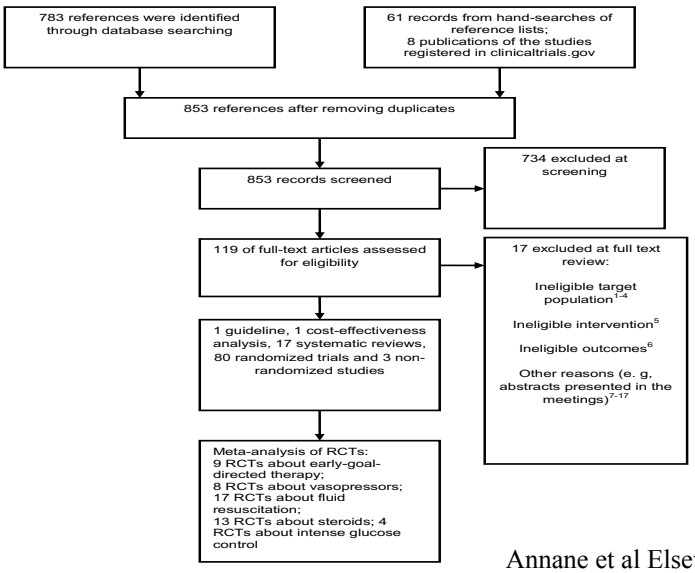
- Start ATB
- Protocolized resuscitation

EGDT IN SEPSIS

	Control	EGDT	RR (95% C.I.)	P-value
In-hospital	**46.5**	**30.5**	**0.58 (0.38-0.87)**	**0.009**
28-day Mortality	**49.2**	**33.3**	**0.58 (0.39 – 0.87)**	**0.01**
60-day Mortality	**56.9**	**44.3**	**0.67 (0.46-0.96)**	**0.03**

Rivers E. *N Engl J Med.* 2001

Systematic review of EGDT

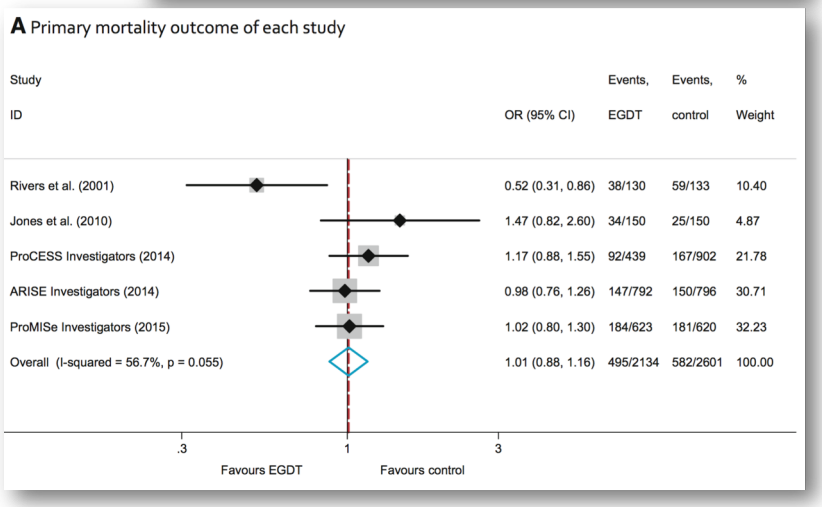


Annane et al Elsevier EBM 2015

Outcomes	Risk with intervention /1000 treated	Risk with control/1000 treated	Relative effect (95%CI) NNT	Number of studies (participants) References	Confidence in the effect estimates (GRADE)	Comments
Early goal-directed fluid and vasopressor therapy (various physiologic goals)						
In-hospital all-cause mortality	238	263	0.9 (0.8;1.1)	8 RCTs (3852)[1-8]	Low	No difference
All-cause mortality, 4 weeks	254	270	0.9 (0.8;1.1)	6 RCTs (4063)[2,3,6-9]	Moderate	No difference
All-cause mortality, >8 weeks	256	264	1.0 (0.8;1.1)	5 RCTs (4012) [3,7,9,10]	Low	No difference
Early goal-directed fluid and vasopressor therapy with guideline recommended targets (Central venous pressure ≥ 8 mmHg; mean arterial pressure (MAP) **>65 mmHg;** central venous oxygen saturation **(ScvO2) ≥ 70%)**						
All-cause mortality, >4 weeks	235	251	RR 0.9 (0.8;1.1)	4 RCTs (4474)[7,8,11,12] and 2 cohort studies(214) [13,14]	Low	No difference
All-cause in-hospital mortality	202	209	RR 0.9 (0.8;1.1)	4 RCTs (4474) [7,8,11,12]	Low	No difference

Annane et al Elsevier EBM 2015

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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Caveats / Limitations of ProCESS, ARISE & Promise

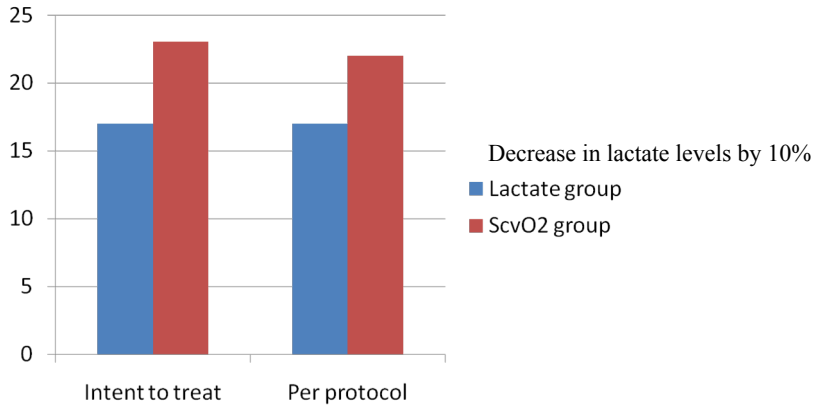
- The overall management of sepsis has changed…
  - In all three studies patients had early antibiotics, > 30ml/kg of intravenous fluid prior to randomization.
- We need therefore to be very careful about over interpreting the results in areas where this paradgim is not valid.

Surviving Sepsis Campaign

The River's work was useful….

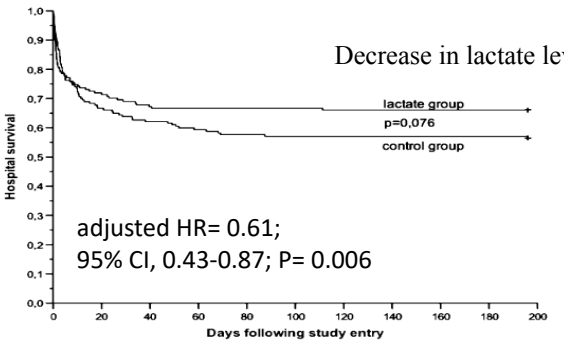
- As it provided us a construct on how to understand resuscitation:
  - Start early- (give antibiotics)
  - Correct hypovolaemia
  - Restore perfusion pressure
  - And in some cases a little more may be required..!
- These concepts are as important today as they ever were.

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy



Jones A. JAMA 2010

Early Lactate-Guided Therapy

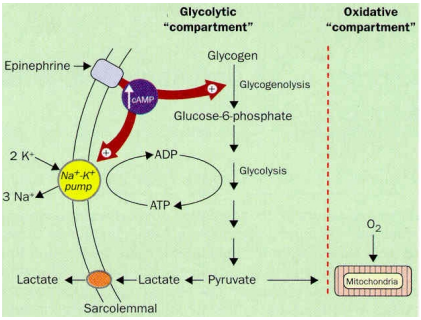


Number at risk:											
Control	177	118	110	105	102	101	101	101	101	101	100
Lactate	171	122	115	114	114	114	113	113	113	113	113

Jansen TC. Am J Respir Crit Care Med 2010

Aerobic production of lactate

- Epinephrine binds to muscle adrenergic β 2 receptors and raises AMP production
  - Activation of sarcolemmal Na+-K+ATPase and increases ADP level
  - Stimulation of glycogenolysis
- Epinephrine increases glycogenolysis with a net increase in pyruvate production and thus an increase in lactate concentration
- ADP increases PFK activity and thus pyruvate production



James et al, Lancet 1999

3 major hemodynamic disorders

hypovolemia → **fluid**

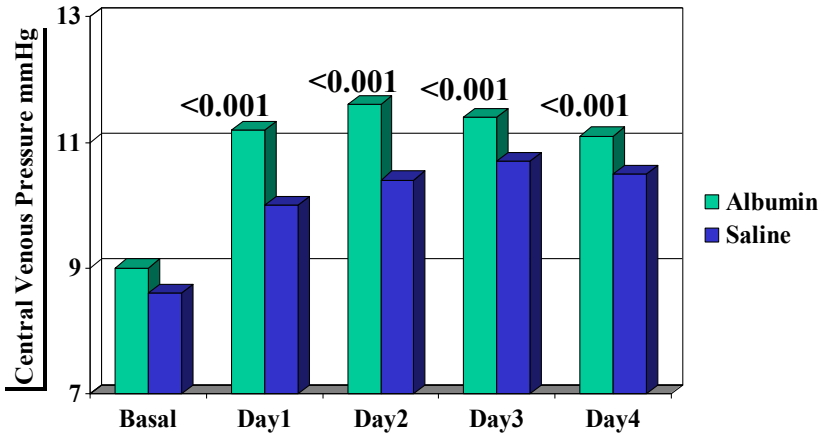
vascular tone depression → **vasopressors**

myocardial depression → **inotropes**

It is important to assess
the degree of each cardiovascular disorder
for applying the best therapy.

Colloids versus Crystalloids

Resuscitation Goals



Finfer et al, NEJM 2004

Table 2. Outcomes and Adverse Events.*

Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03

Mybrugh et al, NEJM 2012

Table 2. (Continued.)

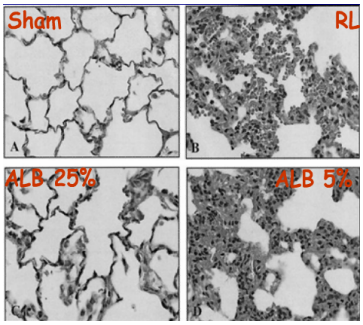
Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Tertiary outcomes§				
Renal-replacement therapy — no./total no. (%)¶	222/903 (24.6)	194/907 (21.4)		0.11
Acute kidney injury — no./total no. (%)‖	183/834 (21.9)	190/837 (22.7)		0.71
Duration of mechanical ventilation — days**			—	0.50
Median	6	6		
Interquartile range	2–14	2–13		
Time to suspension of vasopressor or inotropic agents — days††			—	0.007
Median	3	4		
Interquartile range	1–6	2–7		

Gattinoni et al, NEJM 2014

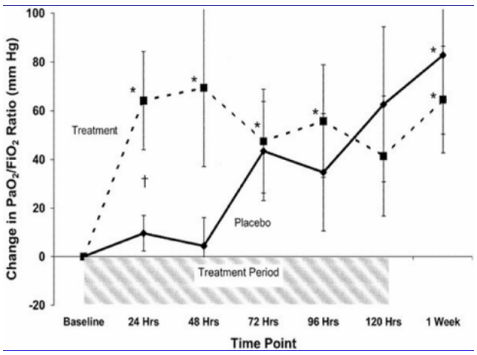
	Colloids N=1414	Crystalloids N=1443	Effect size (95% CI)	P value *
Days alive and free of Vasopressors			**Mean difference**	
within 7 days	5.0 ± 3.0	4.7 ± 3.1	0.3 (-.03;+0.5)	0.041
within 28 days	16.2 ± 11.5	15.2 ± 11.7	1.04 (-0.04;+2.1)	0.033

Annane JAMA 2014

Resuscitation Goals



KA Powers, *Crit Care Med* 2003; 31: 2355



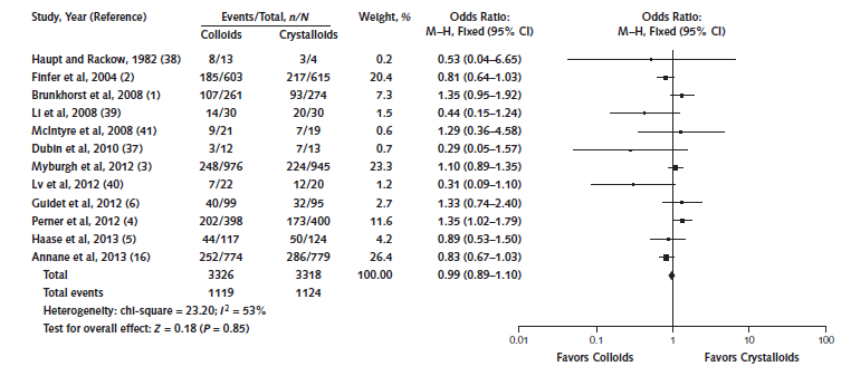
G. Martin, *Crit Care Med* 2002; 30: 2175

	Colloids N=1414	Crystalloids N=1443	Effect size (95% CI)	P value *
Days alive and free of			**Mean difference**	
MV within the first 7 days	2.1 ± 2.4	1.8 ± 2.3	0.3 (0.09; 0.48)	0.010
MV within the first 28 days	14.6 ± 11.4	13.5± 11.5	1.1 (0.14;	0.013

Annane JAMA 2014

Mortality

Appendix Figure 3. **Forest plot for mortality in direct comparisons of all crystalloids vs. all colloids.**



M–H = Mantel–Haenszel.

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Mortality

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

CrI = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.
* Higher of direct or indirect confidence.
† Rated down for imprecision.
‡ Rated down for indirectness.
§ Rated down for inconsistency (I^2 = 80%; P = 0.03 for heterogeneity).
‖ Rated down 2 levels for imprecision.

Rochwerg et al Ann Intern Med 2014

Renal Replacement Therapy

Table 3 Results of four-node network meta-analysis including confidence assessments

Comparison	Number of trials with direct comparisons	Direct estimate (95 % CI)	Indirect estimate (95 % CrI)	NMA estimate (95 % CrI) (higher of direct or indirect confidence)
Starch vs. crystalloid	7	1.39 (1.17, 1.66) H	–	1.39 (1.17–1.66) H
Albumin vs. crystalloid	1	1.04 (0.78, 1.38) M[a]	–	1.04 (0.78–1.38) M
Gelatin vs. crystalloid	0	–	1.05 (0.42, 2.56) VL[b]	1.05 (0.42–2.56) VL
Albumin vs. starch	0	–	0.74 (0.53, 1.04) L[b]	0.74 (0.53–1.04) L
Gelatin vs. starch	1	0.76 (0.31, 1.82) L[a,c]	–	0.75 (0.30–1.81) L
Gelatin vs. albumin	0	–	1.01 (0.38, 2.60) VL[b]	1.01 (0.38–2.60) VL

CI confidence interval, *CrI* credibility interval, *NMA* network meta-analysis, *H* high certainty, *M* moderate certainty, *L* low certainty, *VL* very low certainty

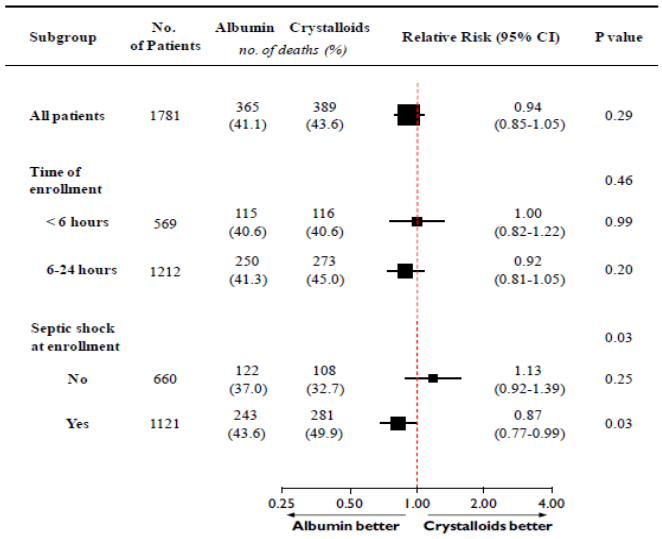
[a] Rated down for imprecision

[b] Rated down for imprecision and indirectness

[c] Rated down for risk of bias

Rochwerg et al Intensive Care Med 2015

Figure S3



Caironi, NEJM 2014

Surviving Sepsis Campaign

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)

Surviving Sepsis Campaign

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**

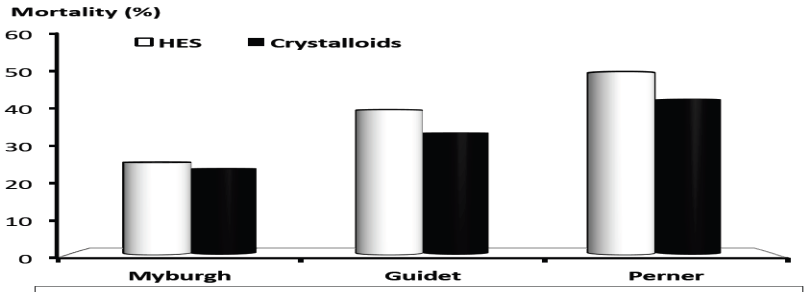
(Strong recommendation, moderate quality of evidence).

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

(weak recommendation, low quality of evidence).

De-escalation

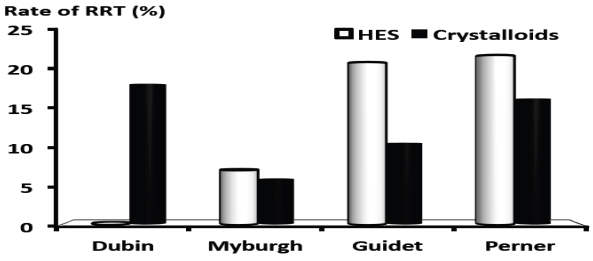
Role of Fluid Balance



Duration	First 4 days	First 4 days	First 3 days
Dose of HES, ml/day (Mean±SD, or M(IQR))	526±425	653(mean)	1500(500-2000)
Net balance of fluids in HES group, ml/day (Mean±SD, or M(IQR))	-61(mean)	0.7/kg (mean)	279(median)
Total amount of fluids in Crystalloid group, ml/day (Mean±SD, or M(IQR))	616±488*	697(mean) *	1500(950-2000)*
	1115±993#	NA#	2095(2094-3780)#

*** Study fluid; # Non-study fluids**
Net balance= the amount of daily positive fluid balance in HES group minus that in crystalloid group
NA=not available

Role of Fluid Balance



Duration	24hr	First 4 days	First 4 days	First 3 days
Dose of HES, ml/day (Mean±SD, or M(IQR))	2610±885	526±425	653(mean)	1500(500-2000)
Net balance of fluids in HES group, ml/day (Mean±SD, or M(IQR))	-3749(mean)	-61(mean)	0.7/kg(mean)	279(median)
Total amount of fluids in Crystalloid group, ml/day (Mean±SD, or M(IQR))	6254±2603	616±488*	697(mean) *	1500(950-2000)*
	2114 ± 726#	1115±993#	NA#	2095(2094-3780)#

*** Study fluid; # Non-study fluids**
Net balance= the amount of daily positive fluid balance in HES group minus that in crystalloid group
RRT= renal replacement therapy
NA=not available

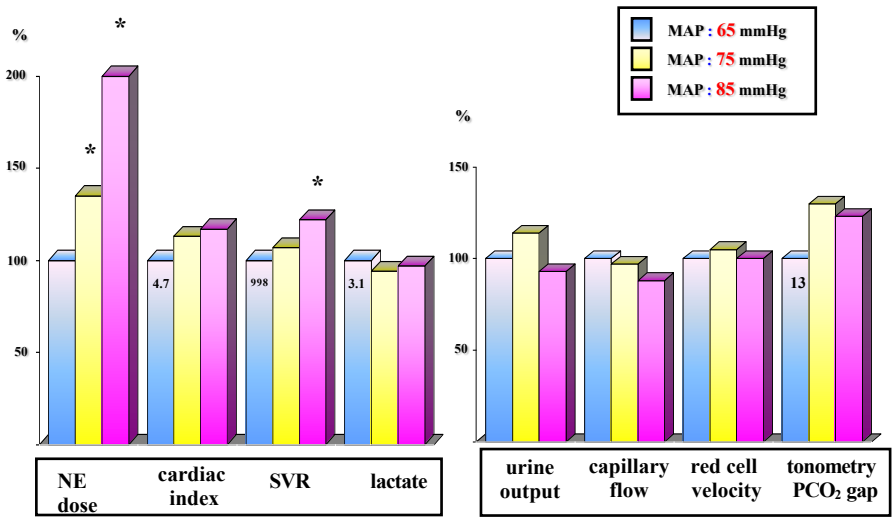
VASOPRESSORS

Blood Pressure Target

Effects of perfusion pressure on tissue perfusion in septic shock

David LeDoux, MD; Mark E. Astiz, MD, FCCM; Charles M. Carpati, MD; Eric C. Rackow, MD, FCCM

Crit Care Med 2000; 28:2729-2732



High versus Low BP Target in Septic Shock

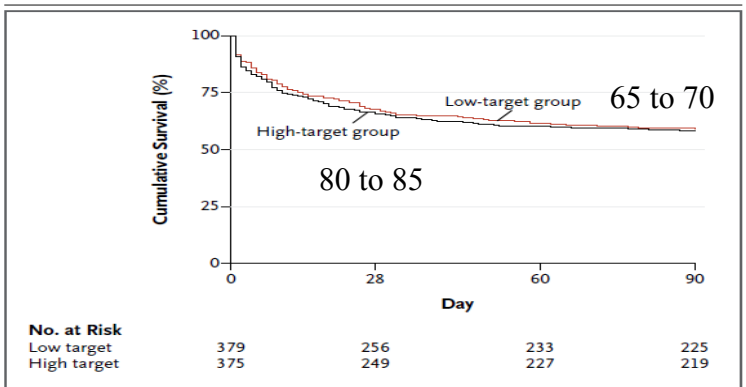


Figure 3. Kaplan–Meier Curves for Cumulative Survival.
Data for the survival analysis, which was performed in the intention-to treat population, were censored at 90 days. There was no significant difference in survival between the high-target group and the low-target group (P=0.57 at 28 days; P=0.74 at 90 days).

Asfar NEJM 2014

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

* Data were available for 1656 patients in the intensive care unit, in the hospital, and at 28 days; for 1443 patients at 6 months; and for 1036 patients at 12 months.
† Odds ratios for death are for the comparison of the dopamine group with the norepinephrine group.

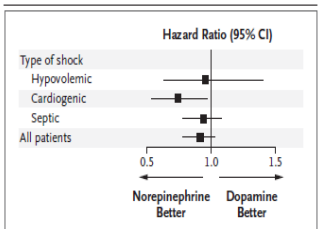


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.
A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

De Backer et al NEJM 2010

Meta-analysis of Norepinephrine versus Dopamine

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Dopamine	Corresponding risk Norepinephrine	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Short-term mortality	**Study population**		**RR 0.91** (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	530 per 1000	**482 per 1000** (440 to 524)			
Serious adverse events - Supraventricular arrhythmias	**Study population**		**RR 0.47** (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	229 per 1000	**82 per 1000** (34 to 195)			
Serious adverse events - Ventricular arrhythmias	**Study population**		**RR 0.35** (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	39 per 1000	**15 per 1000** (8 to 27)			

*The **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

[1] Strong heterogeneity in the results (I squared = 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.
[2] Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, NEJM 2010. We have lowered the quality of evidence one level for indirectness.

Meta-analysis of Norepinephrine versus Epinephrine

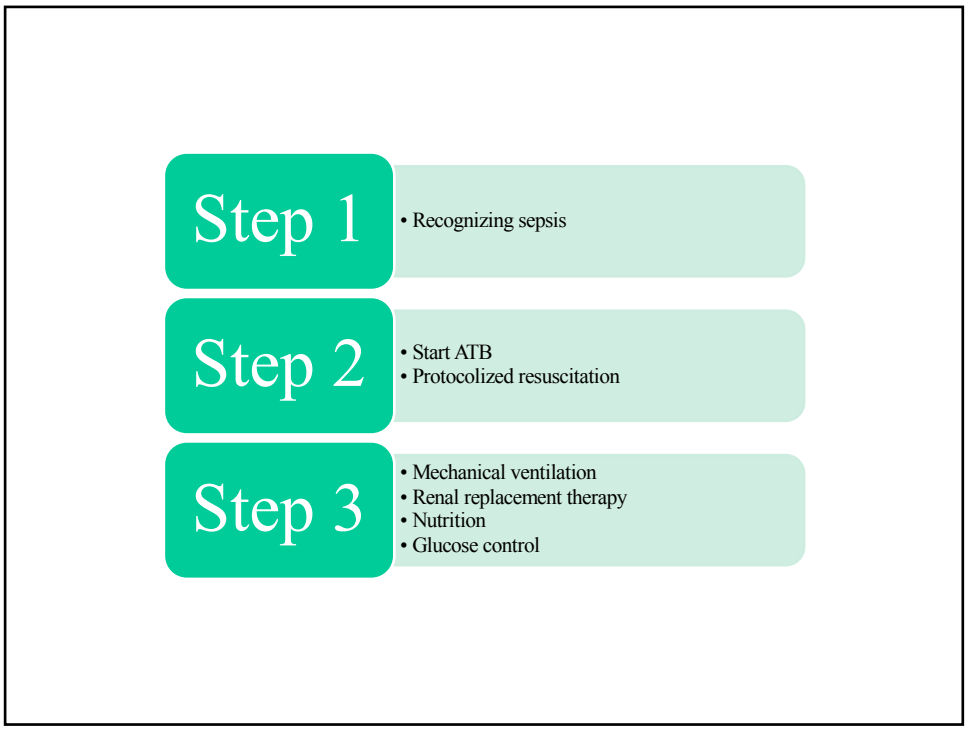
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Epinephrine	Corresponding risk Norepinephrine			
Short term mortality	**Study population**		**RR 0.96** (0.77 to 1.21)	540 (4 studies)	⊕⊕⊕⊖ **moderate**[1]
	357 per 1000	**343 per 1000** (268 to 429)			
Serious adverse events - Supraventricular arrhythmias	**Study population**		**RR 1.10** (0.62 to 1.96)	330 (1 study)	⊕⊕⊖⊖ **low**[1,2]
	118 per 1000	**130 per 1000** (58 to 198)			
Serious adverse events - Ventricular arrhythmias	**Study population**		**RR 0.64** (0.27 to 1.51)	330 (1 study)	⊕⊕⊖⊖ **low**[1,2]
	75 per 1000	**48 per 1000** (-5 to 95)			

[1] Grade reduced for imprecision.
[2] Outcome reported only in one out of four trials.

Meta-analysis of Norepinephrine versus Vasopressin

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Vasopressin	Corresponding risk Norepinephrine			
Short term mortality	**Study population**		**RR 1.12** (0.96 to1.30)	963 (7 studies)	⊕⊕⊖⊖ **low**[1,2,3,4]
	386 per 1000	**433 per 1000** (371 to 502)			
Serious adverse events - Supraventricular arrhythmias	**Study population**		**R.R 7.25** (2.30 to 22.90)	116 (3 studies)	⊕⊕⊖⊖ **low**[1,2,3,5]
	45 per 1000	**325 per 1000** (103 to 1000)			
Serious adverse events - Ventricular arrhythmias	**Study population**		**R.R 0.78** (0.27 to 2.22)	801 (2 studies)	⊕⊕⊖⊖ **low**[1,2,3,4]
	20 per 1000	**15 per 1000** (5 to 43)			
Serious adverse events - Stroke	**Study population**		**RR 1.04** (0.07 to 16.51)	778 (1 study)	⊕⊕⊖⊖ **low**[1,2,3,4]
	3 per 1000	**3 per 1000** (0 to 42)			
Serious adverse events - Acute coronary events	**Study population**		**R.R 1.05** (0.44 to 2.50)	849 (3 studies)	⊕⊕⊖⊖ **low**[1,2,3,4]
	23 per 1000	**24 per 1000** (10 to 58)			
Serious adverse events - Limb ischemia	**Study population**		**R.R 0.54** (0.25 to 1.19)	826 (2 studies)	⊕⊕⊖⊖ **low**[1,2,3,4]
	36 per 1000	**19 per 1000** (-4 to 36)			

[1] Variations in type of molecule (vasopressin vs terlipressin) and in dose.
[2] Some studies have compared vasopressin with norepinephrine and some studies have compared vasopressin plus norepinephrine versus norepinephrine.
[3] Unclear risk of bias in some studies (methods for allocation concealment, blinding).
[4] Imprecision with wide confidence intervals spanning harm and benefit.
[5] Imprecision. Only 21 events.



Surviving Sepsis Campaign

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 PaO_2/FIO_2 ratio <150.**

  (Strong recommendation; moderate quality of evidence)

Surviving Sepsis Campaign

Mechanical Ventilation

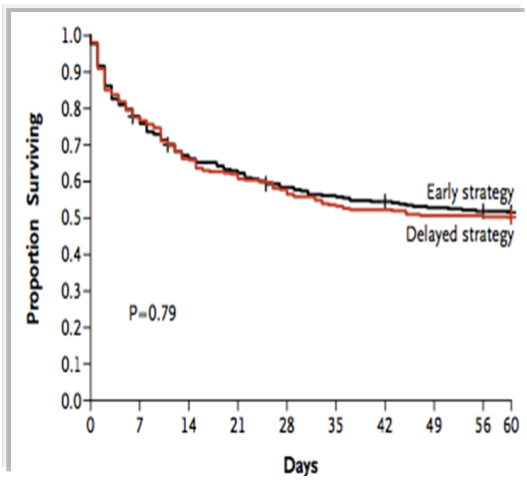
- **We recommend against the use of HFOV in adult patients with sepsis-induced ARDS.**
  (Strong recommendation; moderate quality of evidence)
- **We recommend against the use of beta-2 agonists for the treatment of patients with sepsis- induced ARDS without bronchospasm.**
  (Strong recommendation;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

Surviving Sepsis Campaign

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)

Renal Replacement Therapy



NEJM 2016

Surviving Sepsis Campaign

- **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)

Surviving Sepsis Campaign

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

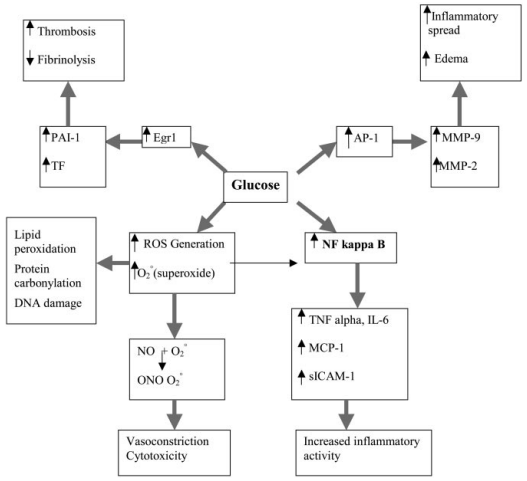
- **We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance.**

(Weak recommendation; low quality of evidence)

Glucose control?

Hyperglycemia injures Central Nervous Sytem

Compromised perfusion



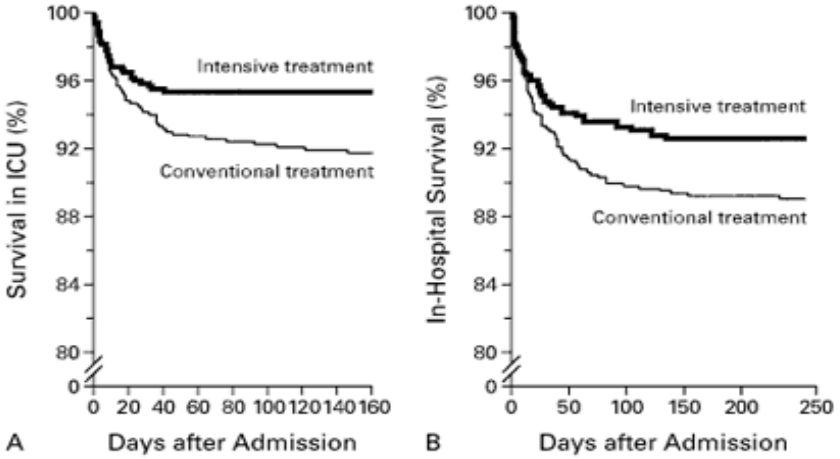
Pro-inflammatory effects

Direct cytotoxicity

Garg, Stroke 2006

Effects of Intensive Insulin Therapy on Survival in Surgical ICU patients.

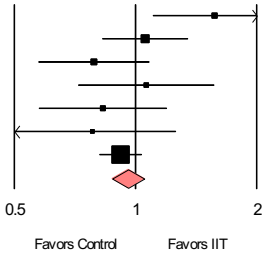
Van den Berghe, NEJM 2002



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Van den Berghe-2001	1.572	1.102	2.242	2.498	0.012
Van den Berghe-2006	1.057	0.826	1.353	0.441	0.659
Glucotrol-2006	0.788	0.573	1.085	-1.460	0.144
VISEP-2008	1.064	0.720	1.572	0.310	0.757
De La Rosa-2008	0.830	0.574	1.199	-0.994	0.320
Arabi-2008	0.781	0.484	1.262	-1.009	0.313
NICE-SUGAR 2009	0.918	0.812	1.038	-1.361	0.173
	0.954	0.871	1.046	-0.995	0.320

Statistics for each study

Odds ratio and 95% CI



Meta Analysis

Energy delivery and BGC

Table 3 Summary of characteristics from the different major trials about glucose-insulin treatment

Study name	VDB 2001 [4]		VDB 2006 [11]		Glucontrol [10]		NICE-SUGAR [5]		COITTSS [7]		VISEP [50]	
	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control
Morning mean BGL, mg/dL	103.6	154.5	110.0	160.9	110.9	140.0	118.0	144.9	147.3	154.5	112.7	152.7
SD or confidence interval	20.0	32.7	30.0	28.0	100-123.6	121.8-160	25.1	26.0	30.9	34.5	1.8	3.6
Death at 90 days, %	5	7	35.9	37.7	23.3	19.4	27.5	24.9	45.9	42.9	39.7	35.4
Caloric intake, kcal/day	550-1,600		1,202	1,237	760	760	891	872	1,350		1,217	1,253
Quantity of glucose administered per day, g	120		202	198	73.7	71.8	23.4	24.4	25		144	144
Daily insulin dose, insulin units	71	33	59	10	31.2	7.68	50.2	16.9	71	46	43	29
SD or confidence interval	48-100	17-56	37-86	0-38	15.6- 55.2	30.48	38.1	29	45-96	30-65	23-64	15-51
Hypoglycemia rate, %	0.8	5	18.7	3.1	8.7	2.7	6.8	0.5	16.4	7.8	10.1	4.1

BGL, blood glucose level; COITTSS, Corticosteroids and Intensive Insulin Therapy for Septic Shock; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation; SD, standard deviation; VDB, Van den Berghe; VISEP, Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

Mazeraud et al Crit Care 2014

Surviving Sepsis Campaign

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)

1. **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)

Surviving Sepsis Campaign

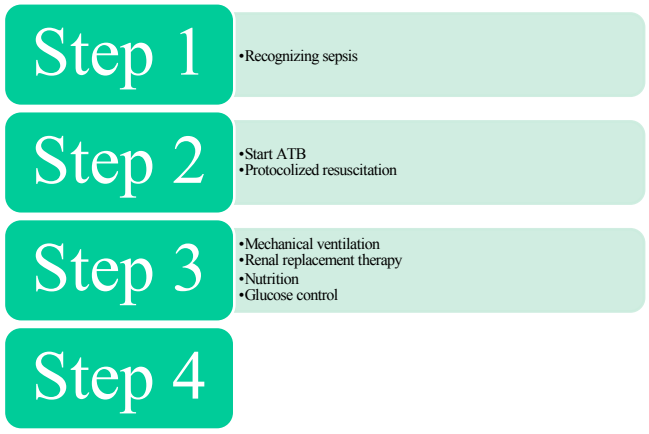
GLUCOSE CONTROL

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)

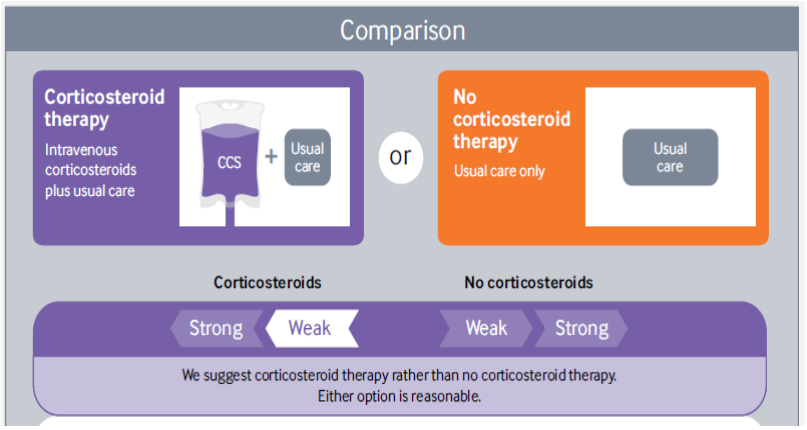
4. **We suggest the use of arterial blood rather than capillary blood for point of care testing using glucose meters if patients have arterial catheters.**

(Weak recommendation; low quality of evidence)

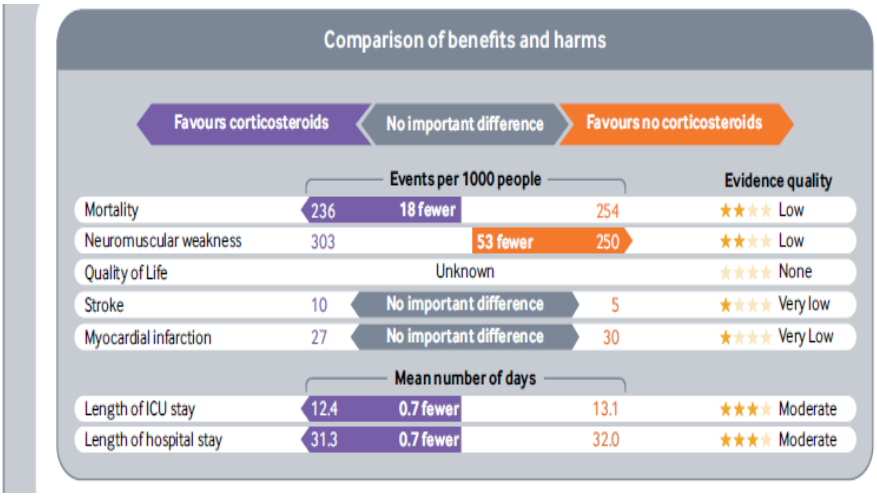


ADJUNCT THERAPIES

Corticosteroids?



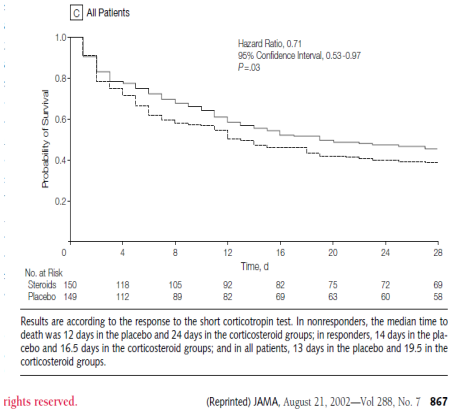
Lamontagne BMJ 2018



Lamontagne BMJ 2018

hydrocortisone + fludrocortisone

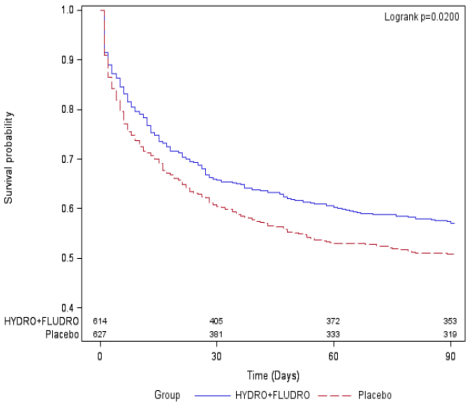
TRIAL 1
N=300



Results are according to the response to the short corticotropin test. In nonresponders, the median time to death was 12 days in the placebo and 24 days in the corticosteroid groups; in responders, 14 days in the placebo and 16.5 days in the corticosteroid groups; and in all patients, 13 days in the placebo and 19.5 in the corticosteroid groups.

Annane Jama 2002

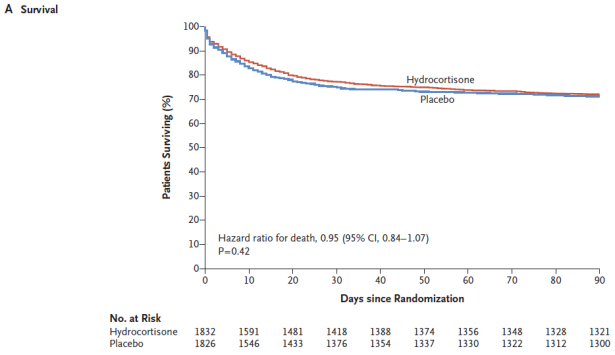
TRIAL 2
N=1241



Annane NEJM 2018

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

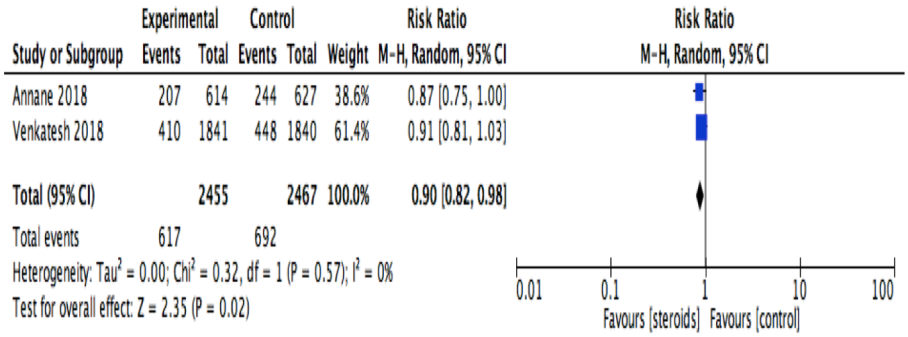
B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*



- N=3658
- HC 200 mg/d IV infusion vs placebo for 7 d or until death or d/c from ICU

NEJM 2018

combined ADRENAL and APROCCHSS



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2018	207	614	244	627	38.6%	0.87 [0.75, 1.00]
Venkatesh 2018	410	1841	448	1840	61.4%	0.91 [0.81, 1.03]
Total (95% CI)		**2455**		**2467**	**100.0%**	**0.90 [0.82, 0.98]**
Total events	617		692			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0\%$

Test for overall effect: Z = 2.35 (P = 0.02)

Rochwerg CCM 2018

IPD Meta-Analysis

Study	Comparison	Deaths (Treatment)	Deaths (Control)	RR
GerInf	Hydro + Fludro vs. Placebo	82	91	0.88
Corticus	Hydro vs. Placebo	86	78	1.04
Coiitss	Hydro + Fludro vs. Hydro	91	102	1

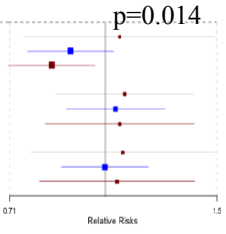
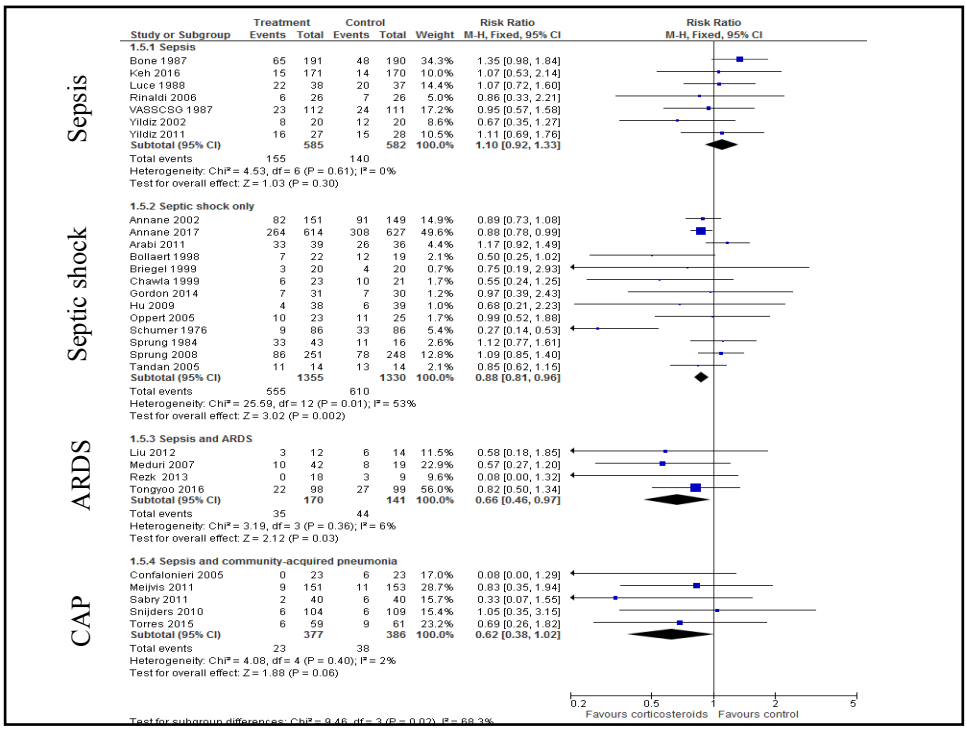


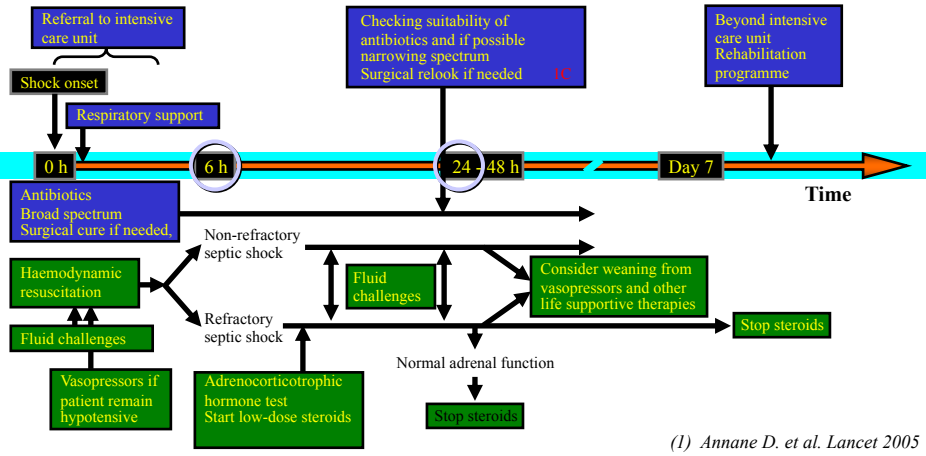
Figure 1: Treatment Effect by Study. For each study, in blue, the effect in the overall population; upper dark red, treatment effect in the responders; lower dark red, effect in the non responders. RR: risk ratio for the overall population

Ger-Inf (n=300); corticus (n=500); coiittss (N=500)

Pirracchio et al, unpublished



Septic Shock Management



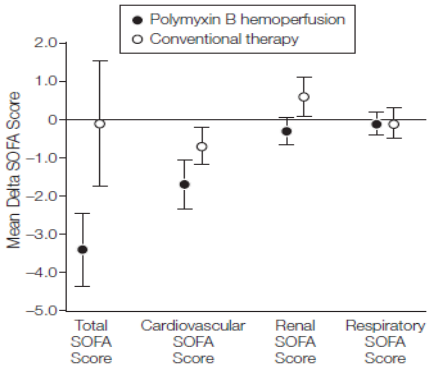
(1) Annane D. et al. Lancet 2005

Curing Sepsis Tomorrow?

Blood Purification?

EUPHAS Trial

Figure 2. Change in SOFA Scores at 72 Hours

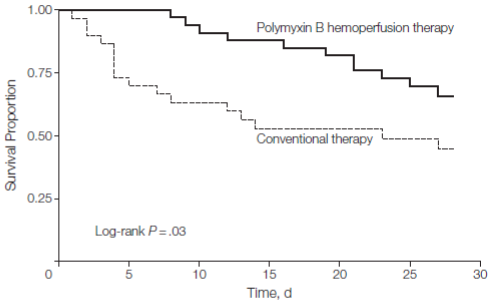


SOFA indicates Sequential Organ Failure Assessment. Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy. Error bars represent 95% confidence intervals. Negative values for delta SOFA scores indicate improvement in organ function, and positive values indicate worsening.

Cruz et al JAMA 2009

EUPHAS Trial

Figure 3. Estimation of Survival Rate According to Treatment Group



No. at risk

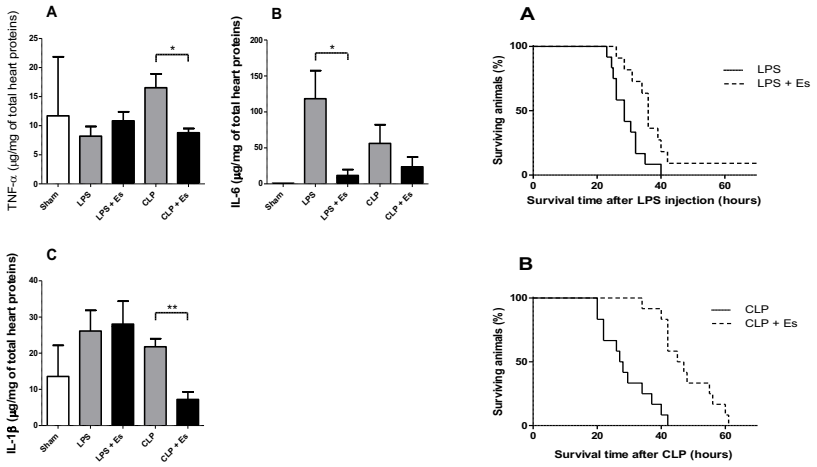
Polymyxin B hemoperfusion therapy	34	34	32	30	27	22	18
Conventional therapy	30	22	19	15	15	12	11

Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

Cruz et al JAMA 2009

Beta-blockade?

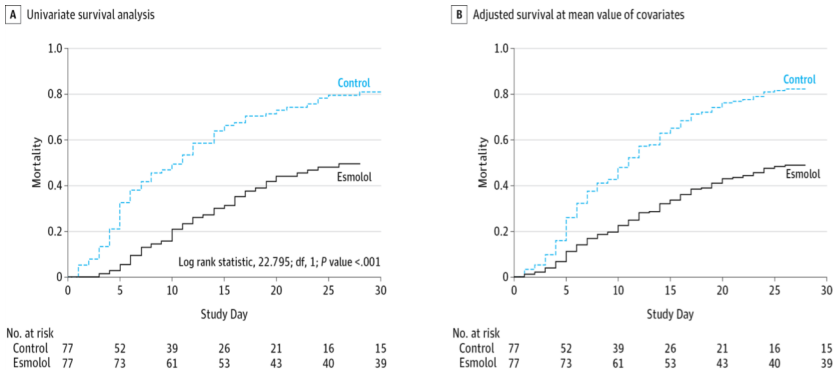
β1 blockers improve survival and provide cardioprotection in septic mice through attenuation of intramyocardial inflammation, chemotaxis and leukocyte endothelial transmigration



The JAMA Network

From: **Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock: A Randomized Clinical Trial**

JAMA. 2013;310(16):1683-1691. doi:10.1001/jama.2013.278477



Cavaillon *et al. Critical Care* 2014, 18:216
http://ccforum.com/content/18/2/216

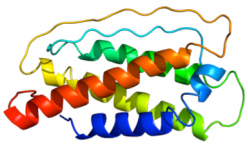
CRITICAL CARE

REVIEW

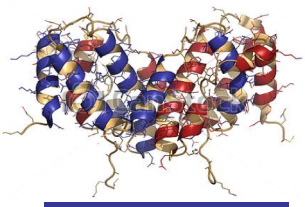
Is boosting the immune system in sepsis appropriate?

Jean-Marc Cavaillon[1*], Damon Eisen[2,3] and Djilalli Annane[4]

GM-CSF



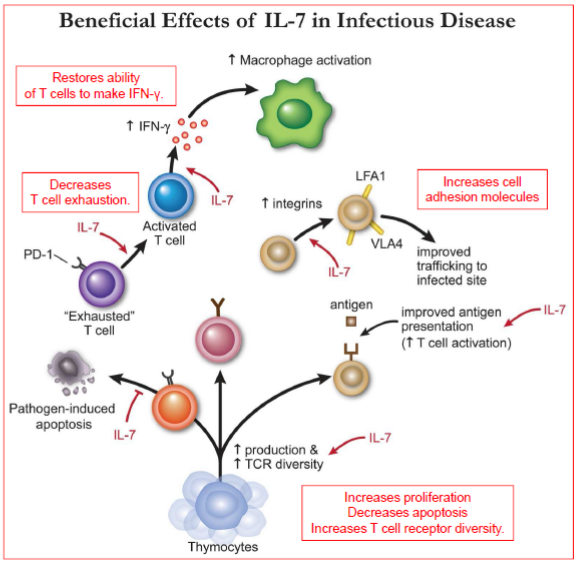
INTERLEUKIN-7



γ–INTERFERON

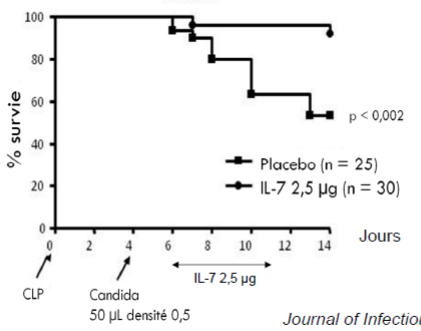
IL-7 acts at multiple levels to improve functionality of CD4 and CD8 T cells and secondarily adaptive immunity.

IL-7 offers a new approach to infectious disease.



IL-7 improves survival in septic mice

IL-7 increases pathogen clearance and improves survival in viral, bacterial, and fungal models
(Unsinger, J Immuol 2010, Kasten, Infect Immun 2010, Unsinger, J Infect Dis 2012)



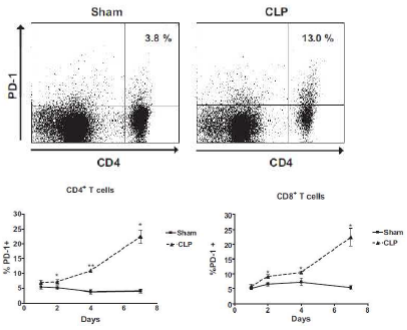
Journal of Infectious Disease, 2012

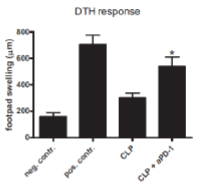
JLB 2010

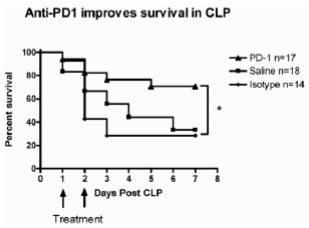
Article

Delayed administration of anti-PD-1 antibody reverses immune dysfunction and improves survival during sepsis

Pavan Brahmamdam,* Shigeaki Inoue,† Jacqueline Unsinger,† Katherine C. Chang,† Jonathan E. McDunn,† and Richard S. Hotchkiss*,†,‡,1







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journal homepage: www.elsevier.com/locate/ijid

Review

Thymosin alpha1 based immunomodulatory therapy for sepsis: a systematic review and meta-analysis

Congcong Li [1], Liyan Bo [1], Qingqing Liu, Faguang Jin *

Department of Respiratory and Critical Care Medicine, Tangdu Hospital, Fourth Military Medical University, Xinsi Road 1, Xi'an, 710038, PR China

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CGITS stage one 2009	23	44	27	47	8.4%	0.91 [0.63, 1.32]
CGITS stage two 2009	44	175	64	167	21.0%	0.66 [0.48, 0.90]
Chen 2007	3	21	9	21	2.9%	0.33 [0.10, 1.06]
Gui 2012	6	22	7	20	2.4%	0.78 [0.31, 1.93]
Huang 2009	13	36	20	34	6.6%	0.61 [0.37, 1.03]
Jianfeng 2013	47	181	63	180	20.3%	0.74 [0.54, 1.02]
Lei 2005	8	21	7	17	2.5%	0.93 [0.42, 2.03]
Li 2009	5	23	13	33	3.4%	0.55 [0.23, 1.33]
Su 2009	26	128	38	114	12.9%	0.61 [0.40, 0.94]
Wu 2004	6	22	12	22	3.9%	0.50 [0.23, 1.09]
Ying 2008	28	59	39	55	13.0%	0.67 [0.49, 0.92]
Zhang 2007	5	19	9	19	2.9%	0.56 [0.23, 1.35]
Total (95% CI)		**751**		**729**	**100.0%**	**0.68 [0.59, 0.78]**
Total events	214		308			

Heterogeneity: Chi² = 6.25, df = 11 (P = 0.86); I² = 0%

Test for overall effect: Z = 5.53 (P < 0.00001)

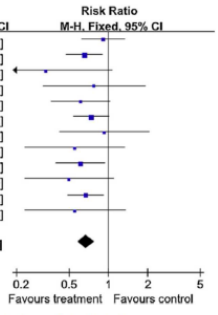

Figure 2. orest plot of the association between tested treatments and mortality among patients with severe sepsis.

Preventing Cognitive Dysfunction

Targets	Intervention	mechanisms
Restoring BBB function	Beta blockade	Endothelial cells and inhibition of MMP9
	Erythropoietin, IVIg, hydrocortisone	Attenuation of in situ cytokines expression
Downregulating microglial cells	IL-1 ra	IL-1 inhibition
	apocynin	Selective inhibition of NADPH oxydase type 2
	mAB 1379 antifactor B	Downregulate oxidative stress
	Anaphylatoxin C5a recombinant	Reduces glutamate toxicity
	minocycline	Downregulate oxidative stress
	Valproic acid	Inhibition of Histone deacetylases

Annane et al Lancet Resp Med 2015

CONCLUSION

Time to Personalized Medicine

A plan of Action From the Round Table

1) More precise identification of target populations—by biochemistry, genetic profiling, phenotype profiling
2) Better tools to detect and track illness that lie closer to the fundamental biology
3) Functional monitoring of hemodynamic response and adequacy of treatment
4) Chronobiologic aspects of critical illness need exploration
5) Chronic critical illness—result of innate disease or the treatments we apply
6) Care withdrawal needs to be better timed
7) Little is known about innate adaptive potential or how best to make use of it
8) Improved methods for Study design (adaptive, etc.) and data analysis
9) Importance of mechanistic understanding prior to trial design and execution
10) Cooperative “open” databases
11) Not too miss the opportunity of big data

Marini J, Vincent JL & Annane D JAMA 2015