Sepsis and septic shock

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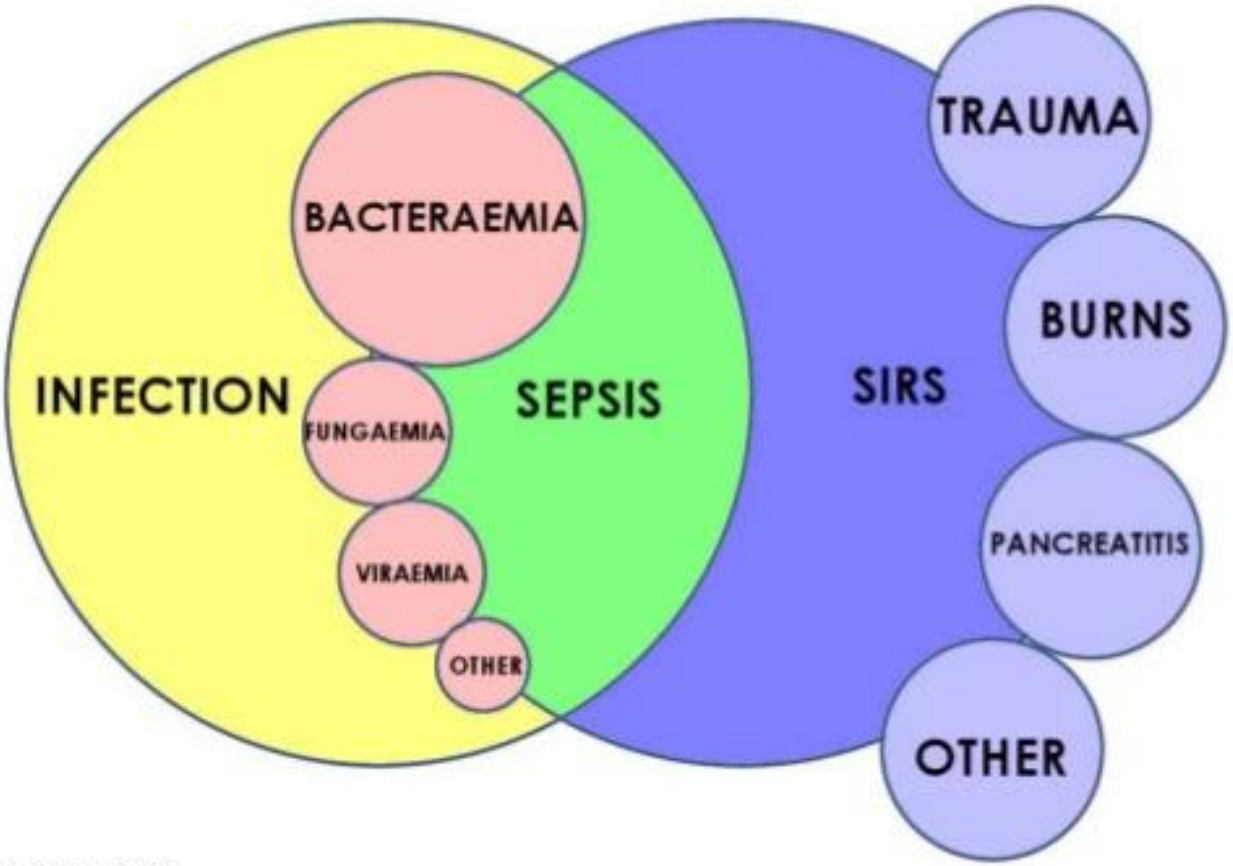
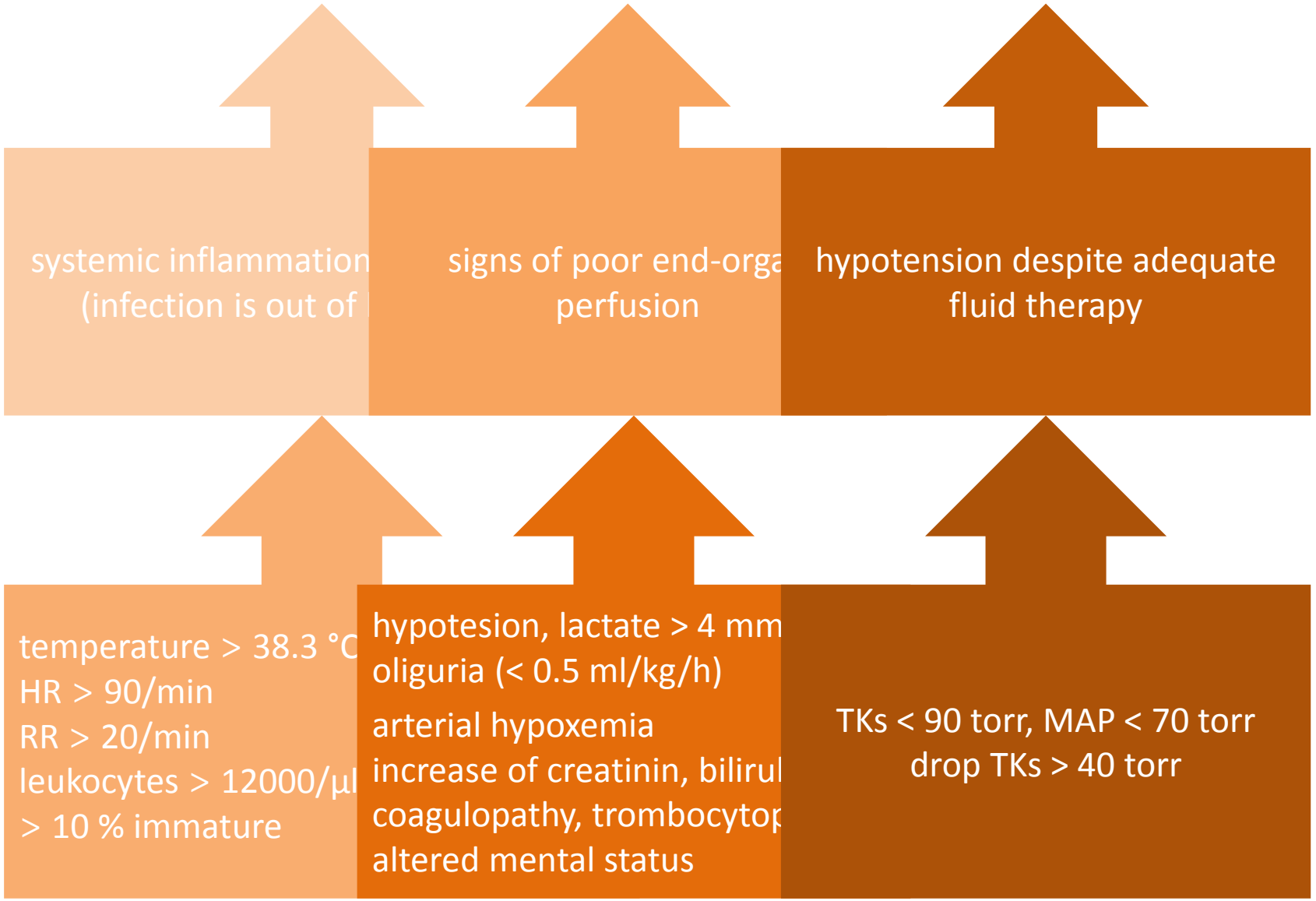
Content

- definition
- diagnosis
- therapeutic targets
- interventions to restore perfusion
- antibiotic therapy
- control of source
- support therapy
- ineffective therapies for sepsis



Adapted from Bone, R. C., Sibbald, W. J., & Sprung, C. L. (1992). The ACCP-SCCM consensus conference on sepsis and organ failure. Chest, 101(6), 1481-3.

infection … sepsis … severe sepsis … septic shock



Diagnosis

- carefull history
- physical examination
- check-up for presence of a **vascular** or urinary catheter
- microbiologic evaluation
- blood cultures
- labs
- chest X-ray
- USG, CT, ECHO, MRI

Labs

CRP

- **increase in 6 – 12 hrs,** max. after 24 – 48 hrs

- do not distinguish sepsis from nonseptic SIRS

- lower levels in malnourished patients

+ suitable for evaluation of antibiotic therapy

PCT

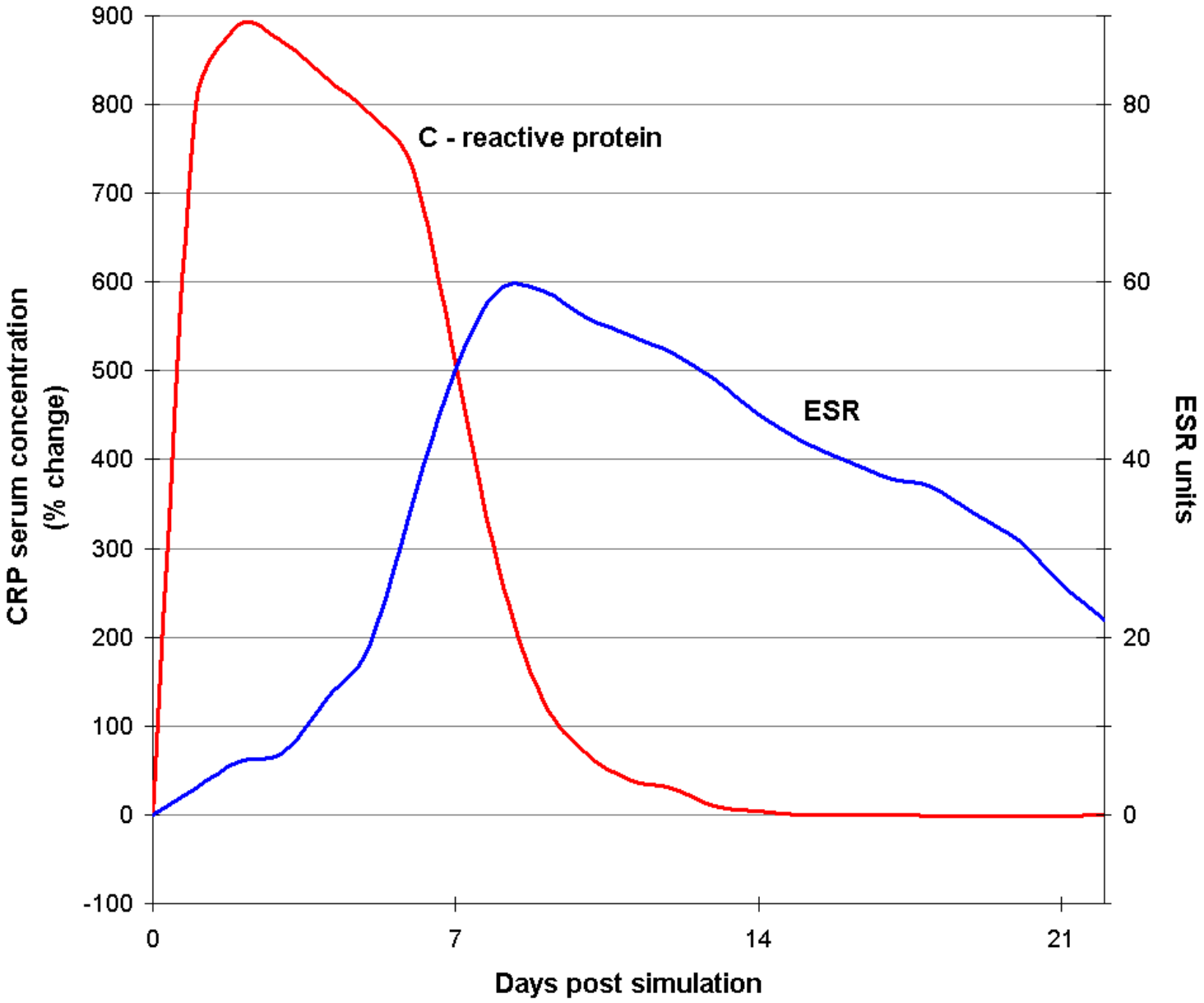
- **increase in 2 – 4 hrs,** max. after 12 – 24 hrs

+ relatively specific for severe sepsis, septic shock (> 10 µg/l)

- not sensitive for localized infection (absces, spondylodiscitis)

IL 6

- **increase in 30 min,** maximum in 6 hrs


900
800
700
600
500
400
300
200
100
0
-100
80
60
40
20
0
0
7
14
21
C - reactive protein
ESR
CRP serum concentration (% change)
ESR units
Days post simulation

„Care bundle“ for severe sepsis

- stabilization of airway and breathing
- establish venous access
- interventions to restore tissue perfusion
- fluids
- vasopressors, inotropes
- red blood cell transfusions
- blood cultures
- early administration of antibiotics
- identification and control of septic focus

Therapeutic targets

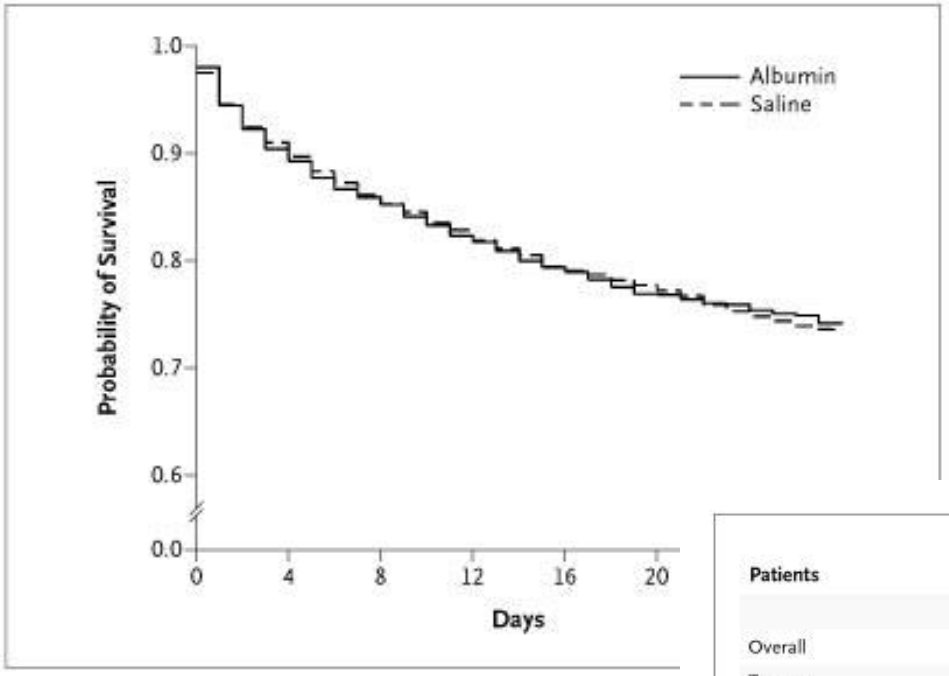
- **MAP > 65 torr**
- **urine output > 0.5 ml/kg/hod**
- ScvO2 ≥ 70 % (or ScO2 ≥ 65 %)
- **CVP 8-12 cm $H_2$0**
- lactate clearance > 10 % (repeat after six hrs)


L'AIGUA ET VA DE MERAVELLA!
A L'ESTIU, BEU ENTRE 2 I 2,5 LITRES AL DIA
Ajuntament de Barcelona

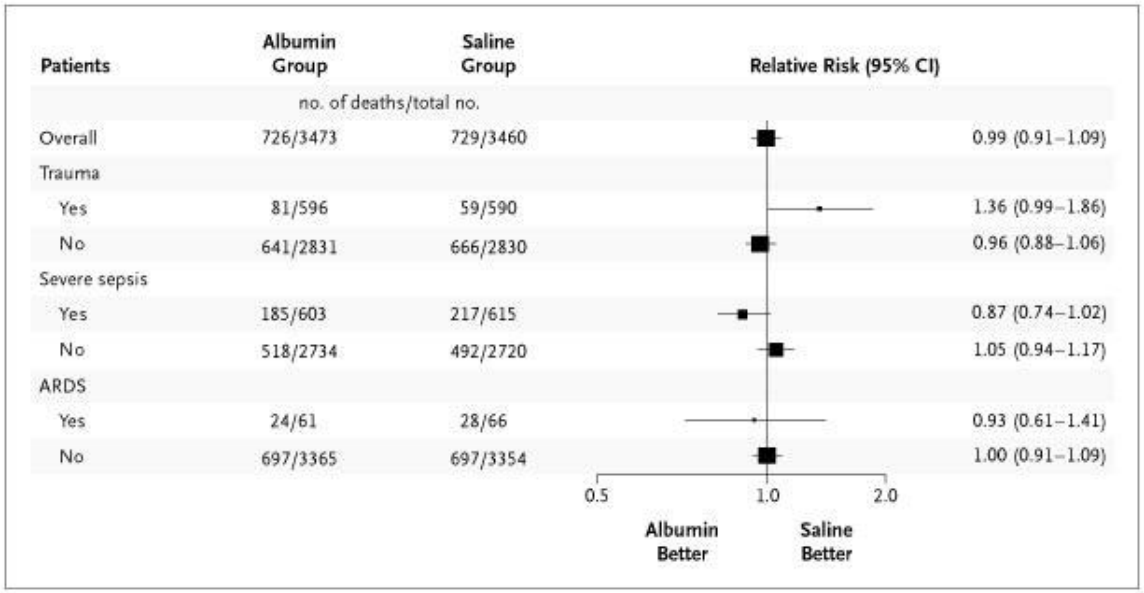
Interventions to restore perfusion - fluids

- early administration of fluid more important than volume
- well-defined rapidly infused boluses (200-300 ml)
- reassess situation after each bolus
- intial fluid challenge can require 3-5 l
- **which fluid ?**

Crystalloids or albumin? (1)



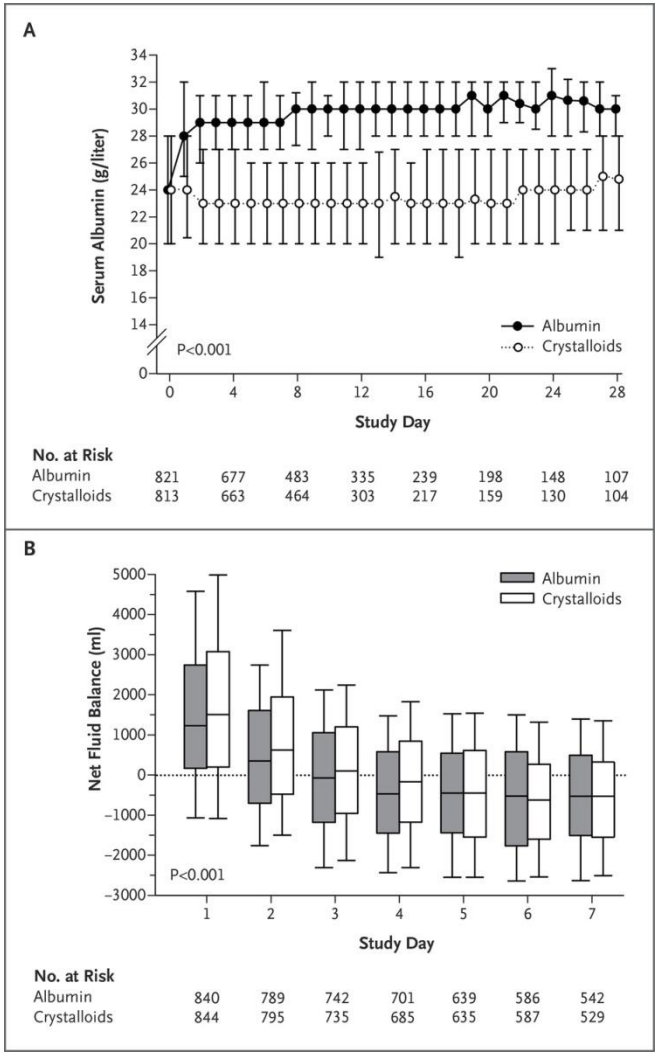
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit (SAFE)
N Engl J Med 2004;350:2247-56

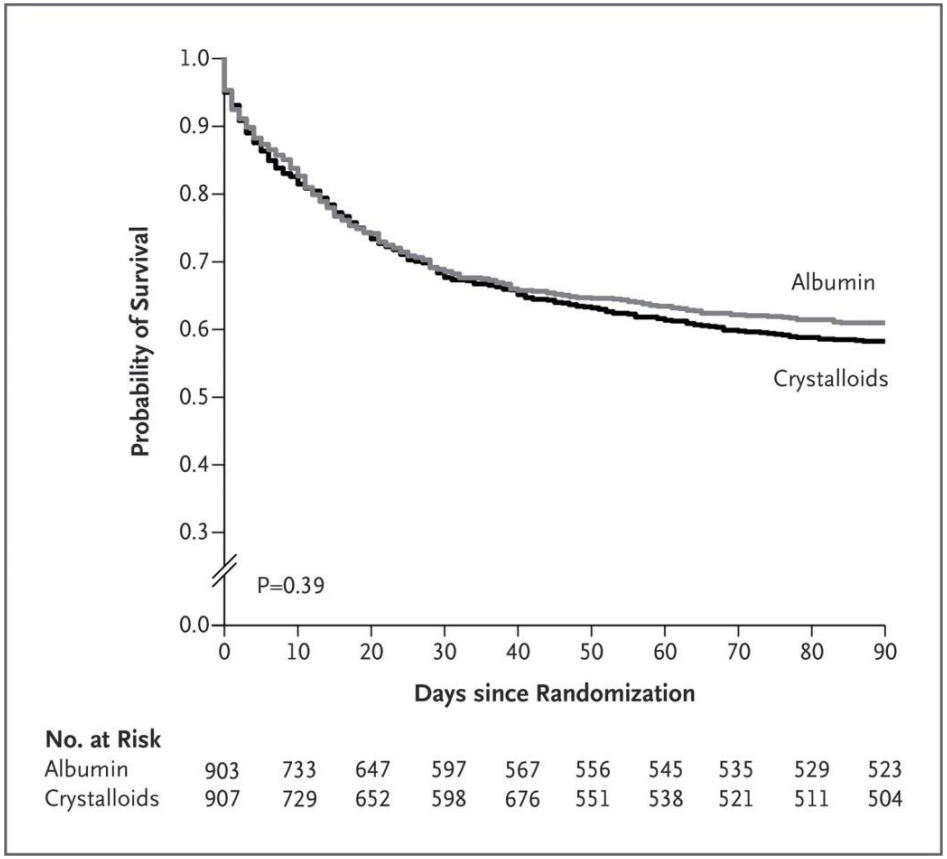


Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)

Crystalloids or albumin ? (2)

Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS)
N Engl J Med 2014;370:1412-21



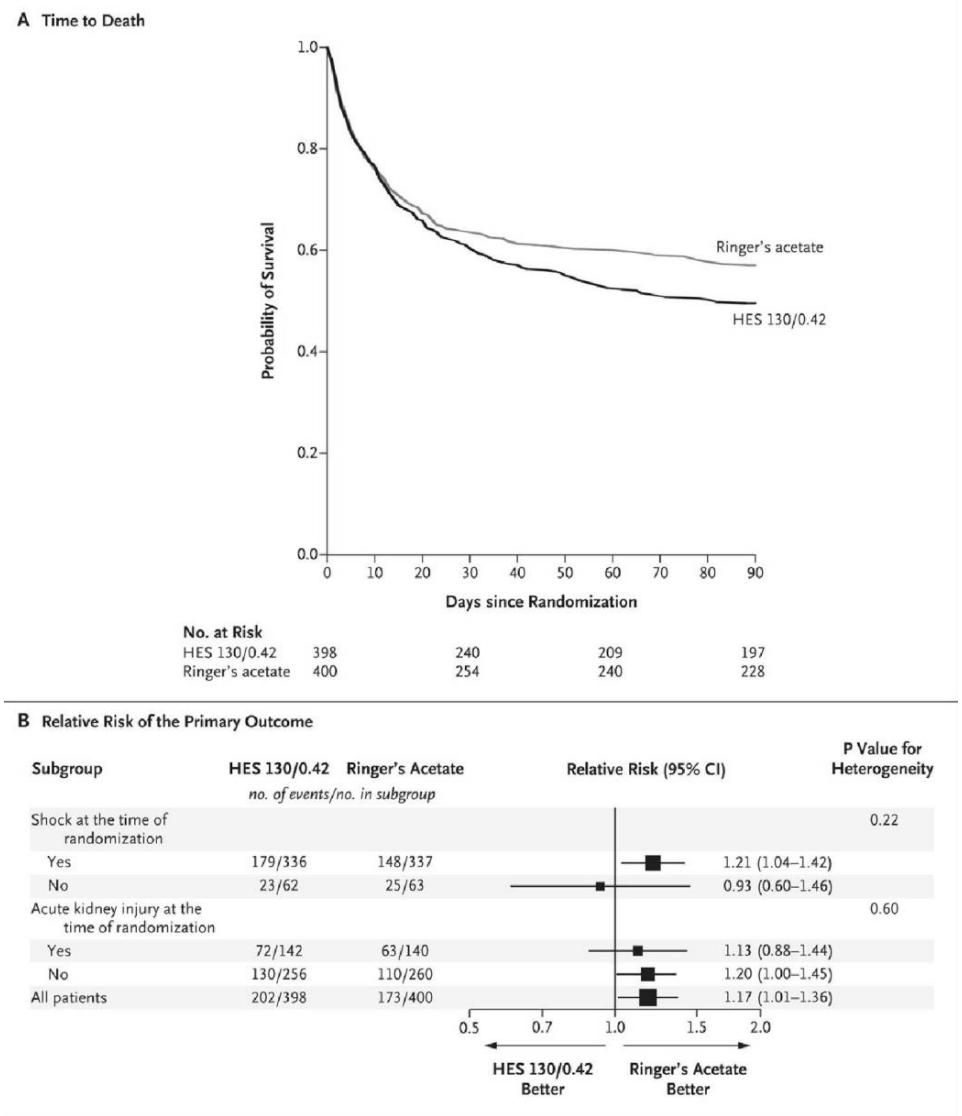


Crystalloids or coloids ?

Scandinavian Starch for Severe Sepsis and Septic Shock (6S) trial

Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis

N Engl J Med. 2012;367(2):124



Crystalloids or coloids ? (2)

- **VISEP** 2008 (HES x Ringer lactate)

  HES – (↑ renal failure, ↑ RRT)
- **6S** 2012 (HES x Ringer acetate)

  HES – (↑ renal failure, ↑ RRT, ↑ mortality)
- **CHEST** 2012 (HES x normal saline)

  HES – (↑ renal failure, ↑ RRT)
- **CRISTAL** 2013 (coloids – gelatins, dextran, HES, albumin x normal saline)

  normal saline – (no difference in mortality in D28, ↑ mortality in D90)

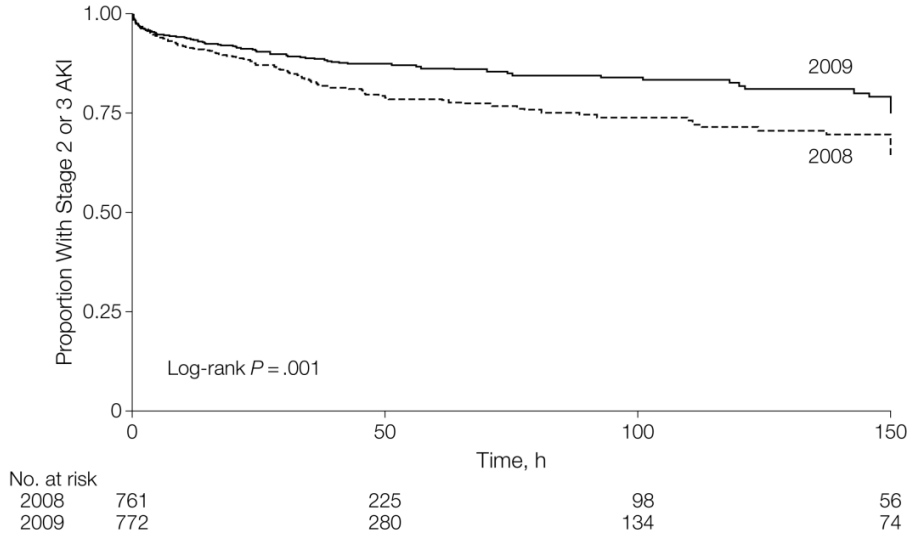
Interventions to restore perfusion - fluids

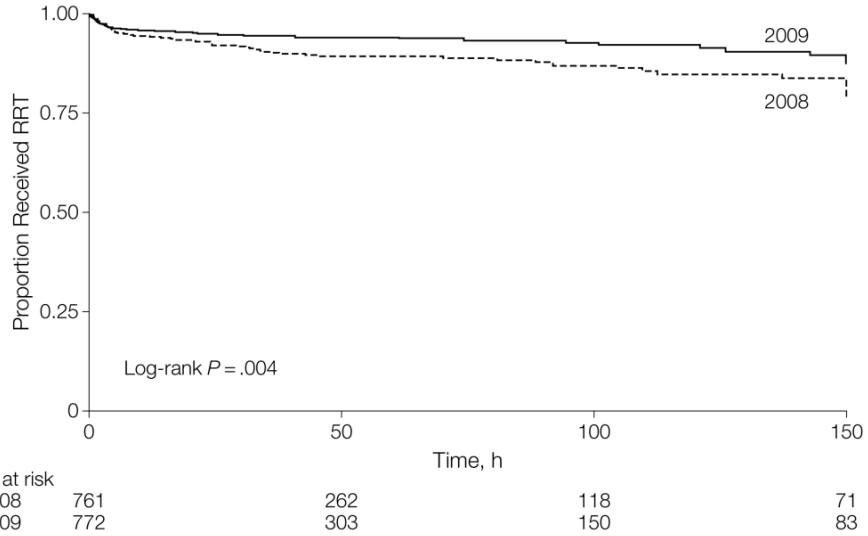
- early administration of fluid more important than volume
- well-defined rapidly infused boluses (200-300 ml)
- reassess situation after each bolus
- intial fluid challenge can require 3-5 l
- **crystalloid solutions**
  - **– which ?**

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

JAMA. 2012;308(15):1566-1572.

The chloride-restrictive strategy was associated with a significantly lower increase in serum creatinine level during ICU stay of 14.8 µmol/L (95% CI, 9.8-19.9 µmol/L) during the intervention period vs 22.6 µmol/L (95% CI, 17.5-27.7 µmol/L) during the control period (*P* = .03; adjusted *P* = .007).





Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis

Crit Care Med. 2014 Jul;42(7):1585-91

Outcome	balanced Fluid–Matched Cohort	No-balanced Fluid–Matched Cohort	Effect Estimate	95% CI
Absolute in-hospital mortality	19.6% (659 of 3,365)	22.8% (768 of 3,365)	Relative risk, 0.86	0.78, 0.94; p = 0.001
ARF with dialysis	4.52% (142 of 3,144)	4.74% (149 of 3,144)	Relative risk, 0.953	0.761, 1.194
ARF without dialysis	7.12% (159 of 2,655)	7.50% (199 of 2,655)	Relative risk, 0.950	0.784, 1.150
Hospital LOS in days (survivors)	11.26	11.37	Absolute difference, –0.11	–0.55, 0.34
ICU LOS in days (survivors)	5.39	5.50	Absolute difference, –0.11	–0.37, 0.15

ARF = acute renal failure, LOS = lengths of stay.
Analyses compare patients initially treated with balanced fluids with patients not treated with any balanced fluids and estimate effects on all outcomes (occurring beyond day 2).
Relative risks for in-hospital mortality (p = 0.001),
ARF (with and without dialysis), and absolute differences in ICU and hospital LOS among survivors are reported.
ICU LOS was significantly lower in sensitivity analyses (including outcomes occurring on and beyond day 2), whereas other results remained consistent

Interventions to restore perfusion - fluids

- early administration of fluid more important than volume
- well-defined rapidly infused boluses (200-300 ml)
- reassess situation after each bolus
- intial fluid challenge can require 3-5 l
- **crystalloid solutions – <u>ballanced</u>**
- **albumin can be added**
- **starch may be harmful**

Interventions to restore perfusion vasopressors, inotropes

- indication – hypotension despite adequate fluid therapy
- **norepinephrine** (0.01-3 µg/kg/min)
- second line agents - epinephrine (0.01-0.5 µg/kg/min) or vasopresin (0.01 IU/min) *or terlipresin*
- inotropes - dobutamin (1-20 µg/kg/min) or levosimendan in patients with cardiac dysfunction (preexisting or acute – septic cardiomyopathy)

Vasoactive agents in septic shock

Drug	Effect on heart rate	Effect on contractility	Arterial constriction effects
Dobutamine	+	+++	- (dilates)
Dopamine	++	++	++
Epinephrine	+++	+++	++
Norepinephrine	++	++	+++
Phenylephrine	0	0	+++
Amrinone	+	+++	-- (dilates)

Interventions to restore perfusion red blood cell transfusions

Indications:

- anemia Hb < 70 g/l
- ScvO2 remains <70 percent after optimization of intravenous fluid and vasopressor therapy

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

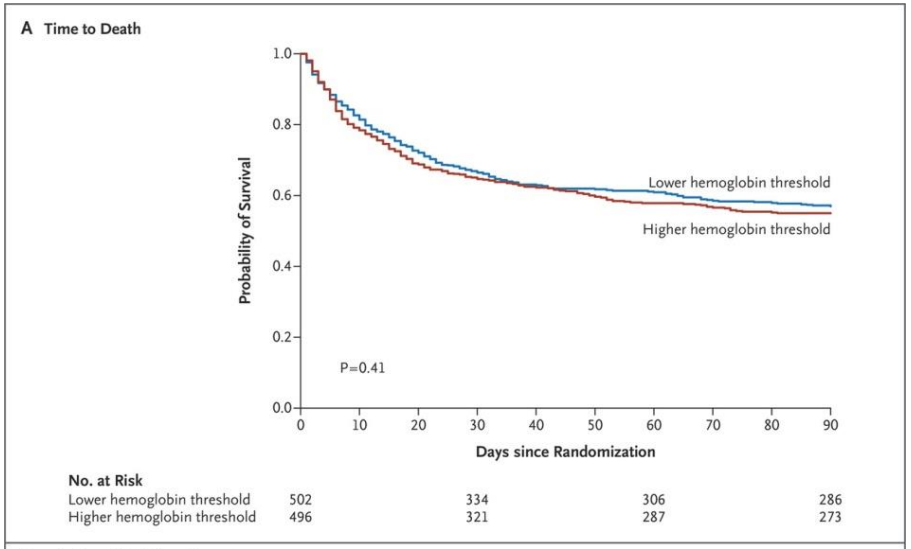
N Engl J Med. 2014 Oct 9;371(15):1381-91

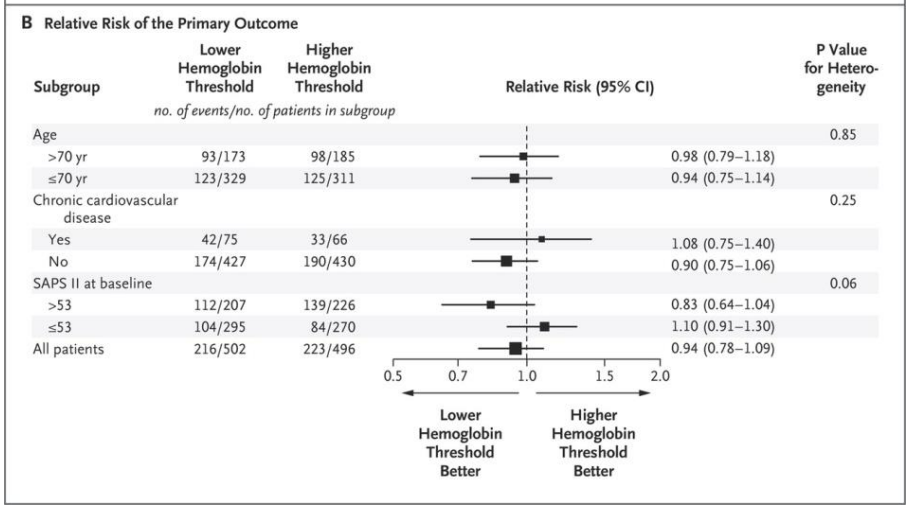
Treshold 70 g/l vs. 90 g/l

Treshold 70 g/l: less transfusions

No difference in mortality

No difference in ischemic events

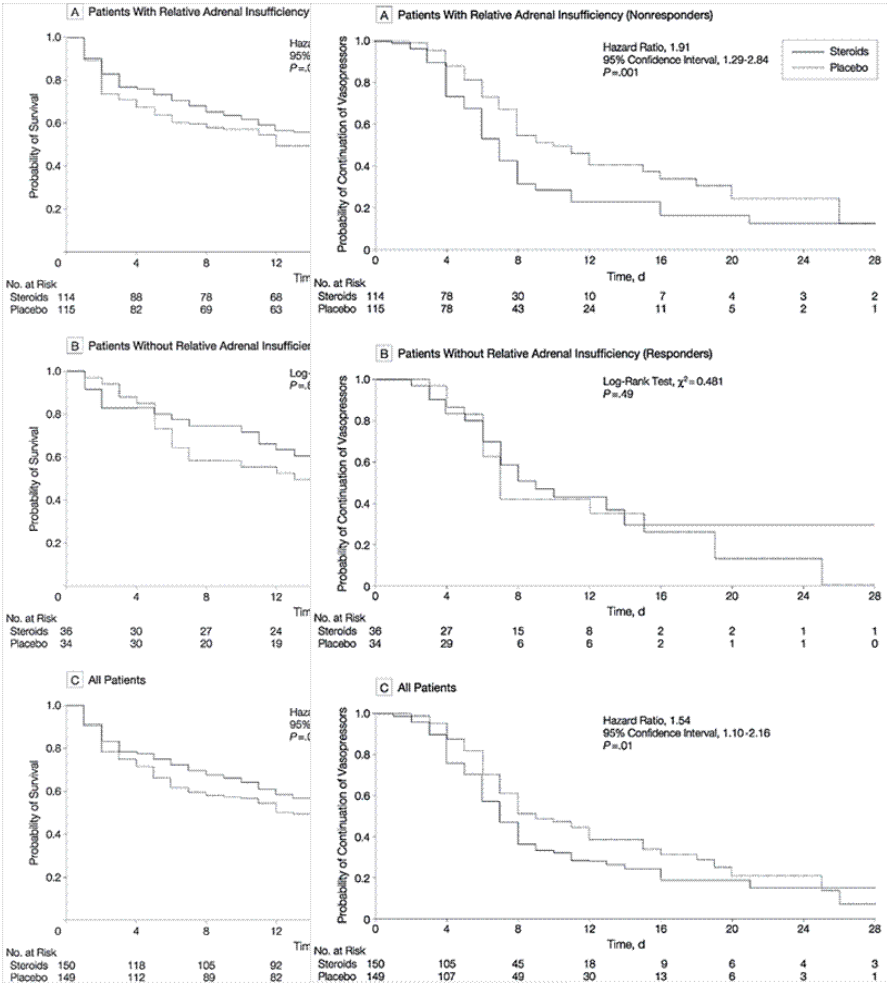




Corticosteroid therapy (1)

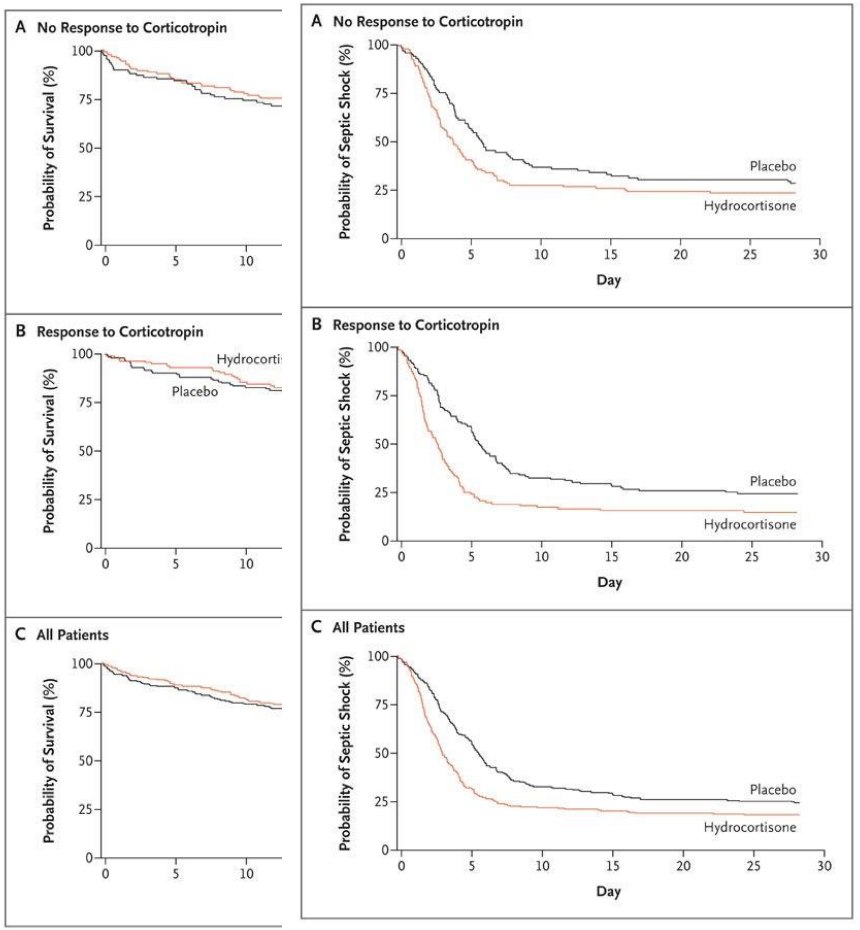
Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

JAMA . 2002;288:862-871



Hydrocortisone Therapy for Patients with Septic Shock (CORTICUS)

N Engl J Med 2008; 358:111-124



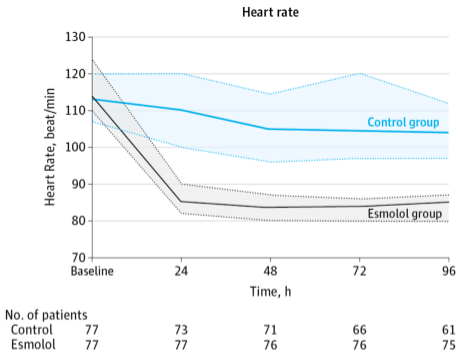
Corticosteroid therapy (2)

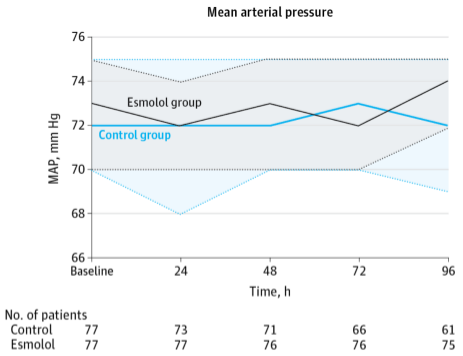
- indication - severe septic shock unresponsive to adequate fluid resuscitation and vasopressors
- no impact on mortality
- ↓ consumption of vasopressors
- no indication in sepsis without shock
- 200 mg hydrocortison/day – continuous administration
- tapering of corticosteroids after end of vasopressor therapy

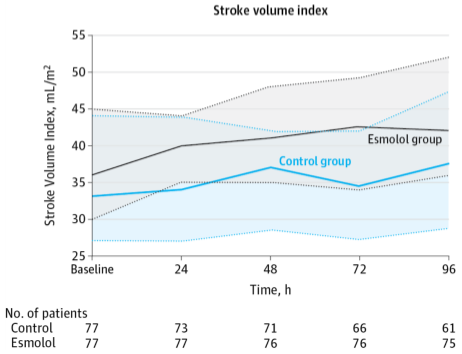
Control of tachycardia – esmolol (1)

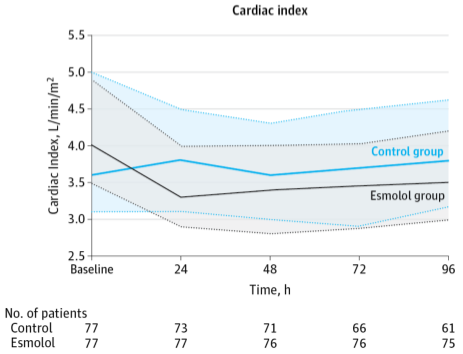
Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
JAMA. 2013;310(16):1683-1691

- ↓ heart rate
- safe therapy
- no negative effect on hemodynamics
- ↓ dose of norepinephrine
- ↓ mortality needs more investigation

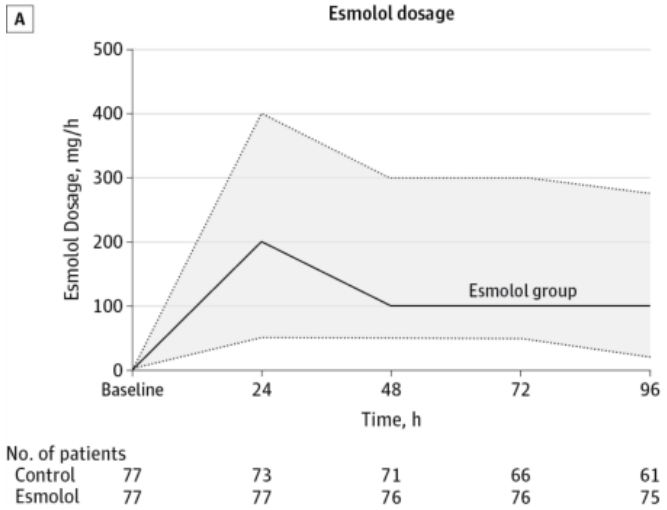


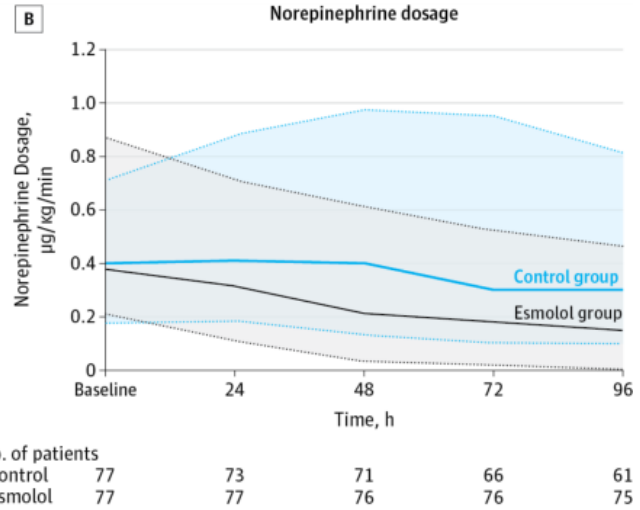


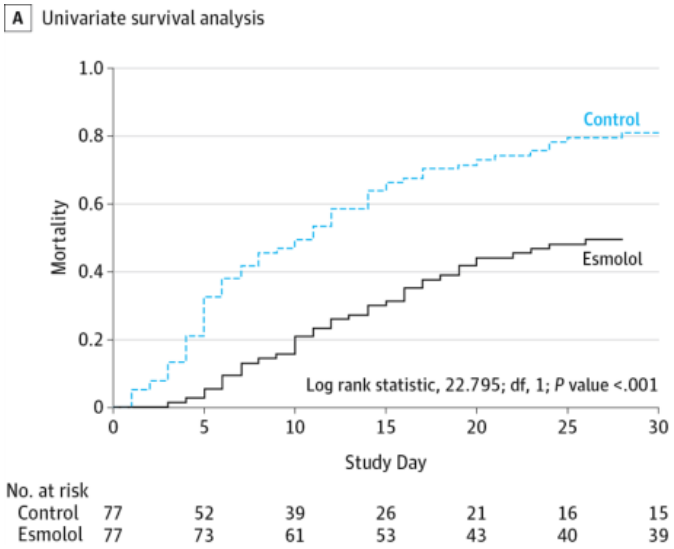


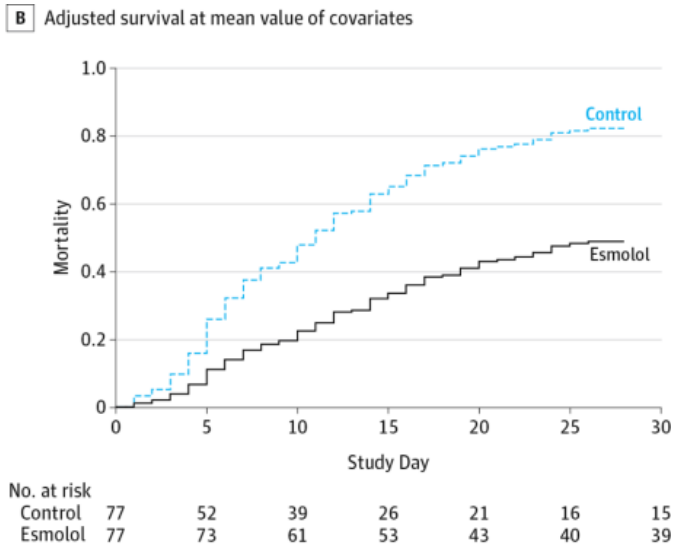


Control of tachycardia – esmolol (2)









Antibiotic therapy (1)

Hit early

- early initiation of antibiotic therapy
- time to initiation – strong predictor of mortality !

Hit hard

- combination therapy i.v.
- consider patient´s history and clinical context
- according to culture results - pathogen- and susceptibility-directed
- de-escalation

Antibiotic therapy (2)

community-acquired infection

- 3rd or 4rd generation cephalosporin (cefotaxime, ceftazidime, ceftriaxon, cefepime)

  or
- beta-lactam+beta-lactamase inhibitor (piperacillin+tazobactam, ticarcillin+clavulanate)

  or
- carbapenem (meropenem, imipenem)

  +
- aminoglycoside (gentamicin, amikacin)

Antibiotic therapy (3)

hospital-acquired infection

- 4rd generation cephalosporin (cefepime)

  or

- beta-lactam+beta-lactamase inhibitor (piperacillin+tazobactam)

  or

- carbapenem (meropenem, imipenem)

  +

- aminoglycoside (gentamicin, amikacin)

  +

- vancomycin (until the possibility of MRSA sepsis has been excluded)

Antibiotic therapy (4)

- ↑ resistence (even) in community
- G+ pathogens (MRSA, VRSA)
- G- pathogens (ESBL, cefalosporinase AmpC – Klebsiella, E. coli, Pseudomonas)
- the most reliable therapy in severe sepsis:

meropenem 1-2g/6-8hrs or imipenem 1g/6hrs

+ amikacin 1.5-2 g QD

+ vancomycin (until the possibility of MRSA sepsis has been excluded)

Errors in antibiotic therapy

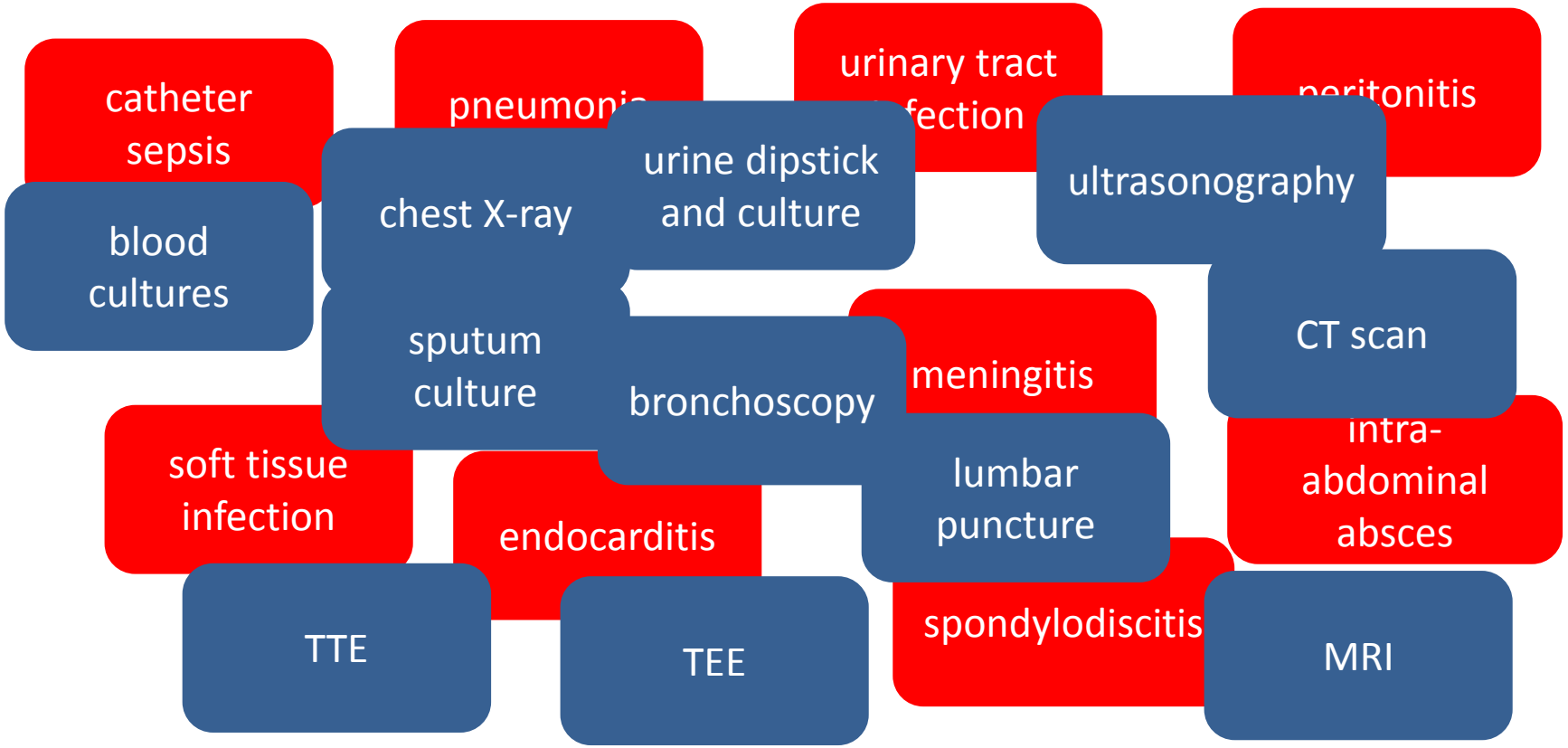
- late initiation of therapy
- start of ATB before blood cultures
- only 1 pair of blood cultures
- inadequate dose
- disregarding toxicity
- excessively duration of therapy
- omission of possible yeast ethiology

Always consult mikrobiology department

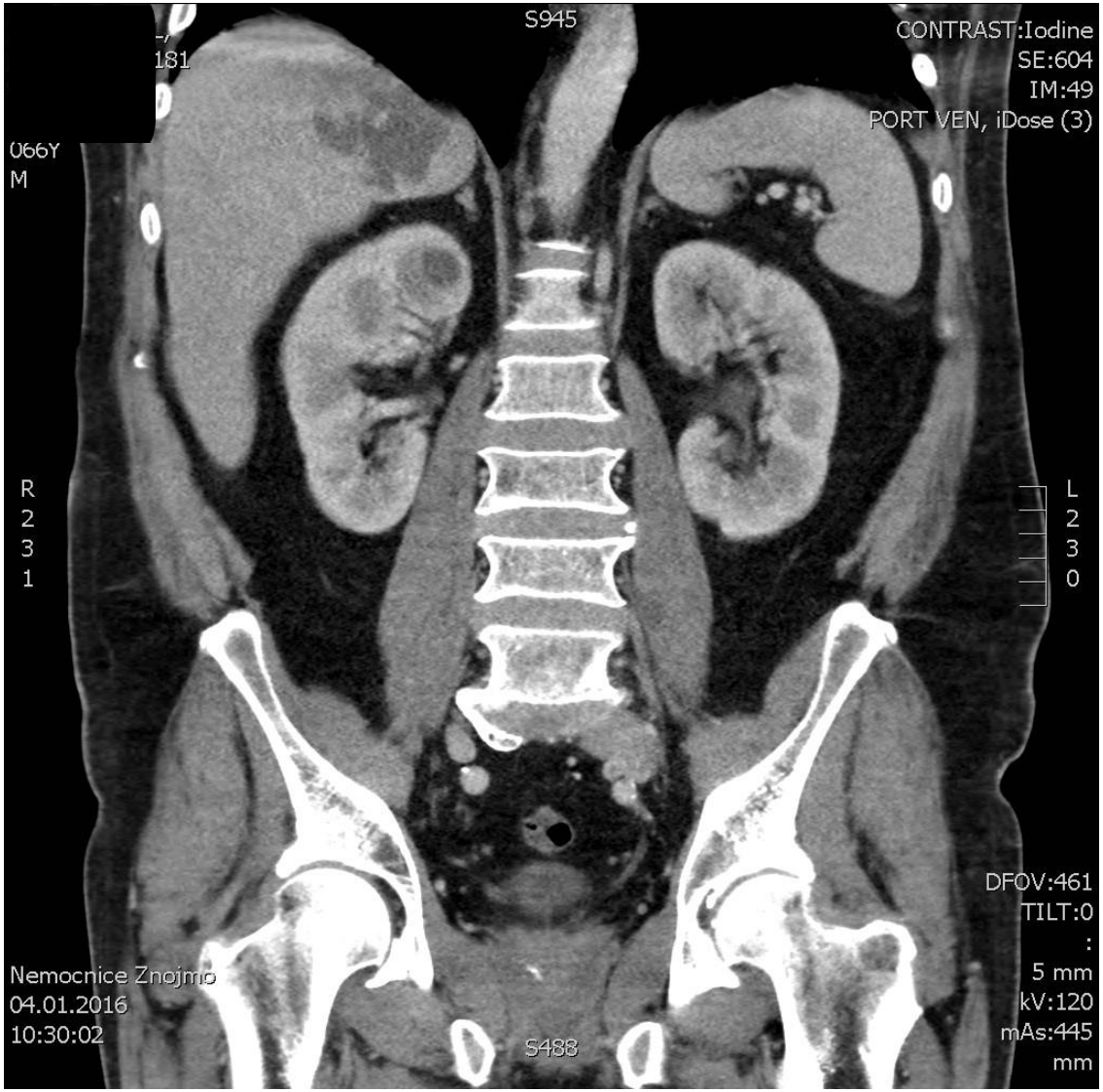
Identification and control of septic focus

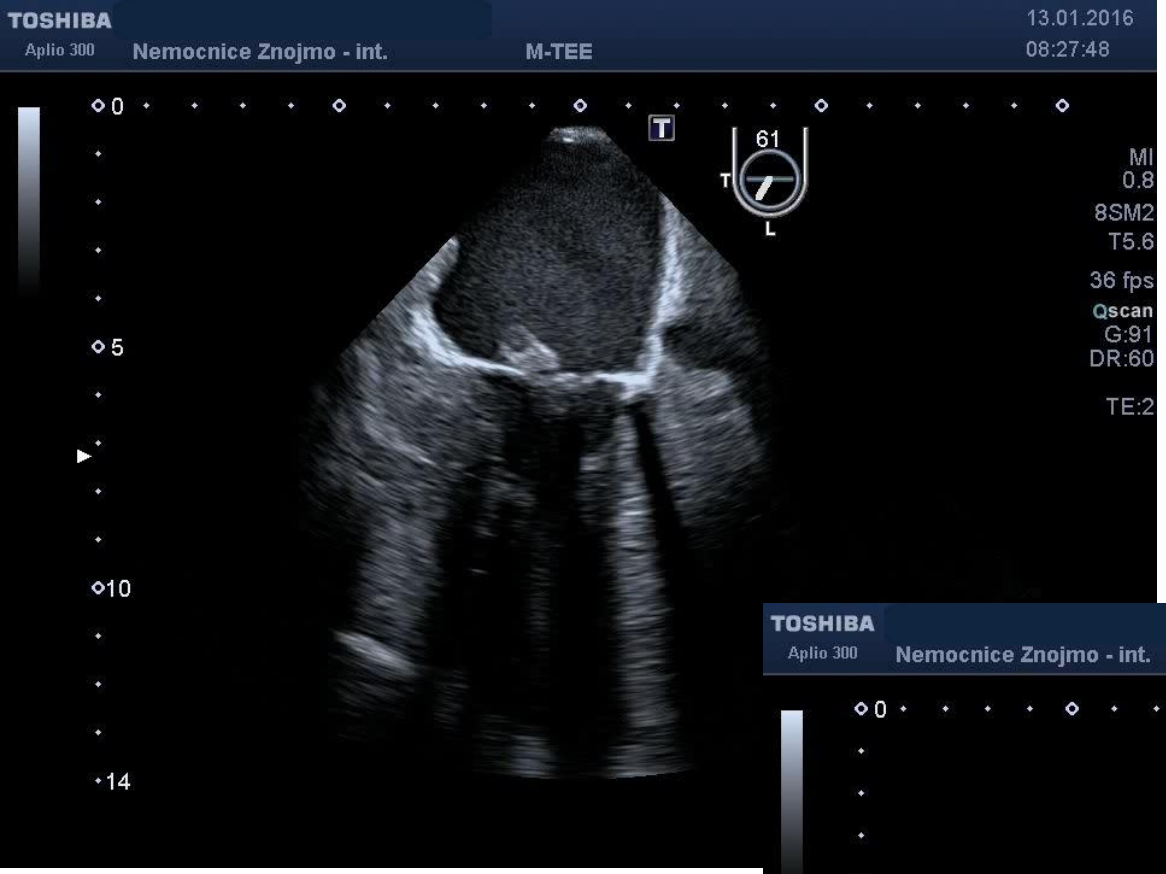
- prompt **identification** and **treatment** of the primary site of infection are essential
- BC, sputum and urine for Gram stain and culture
- remove vascular access devices
- do more investigations ……

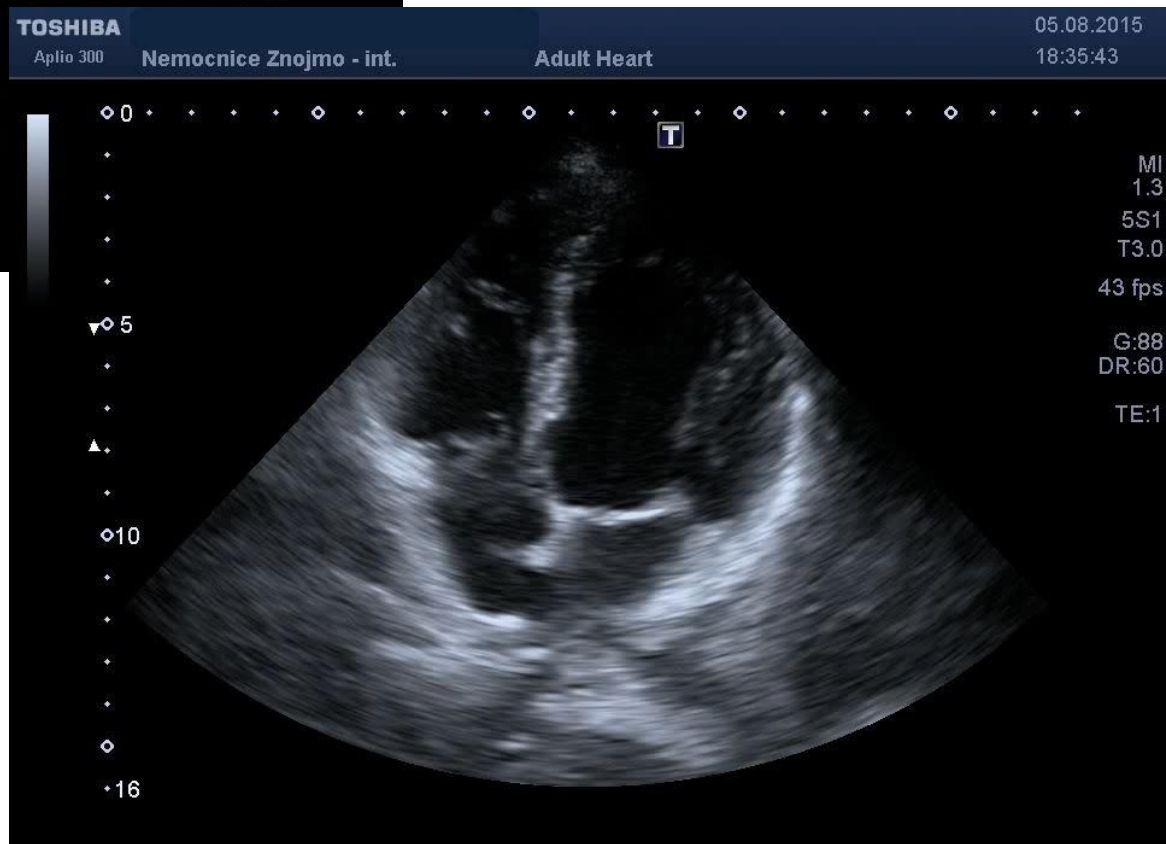
Diagnostic procedures to identify primary site of infection

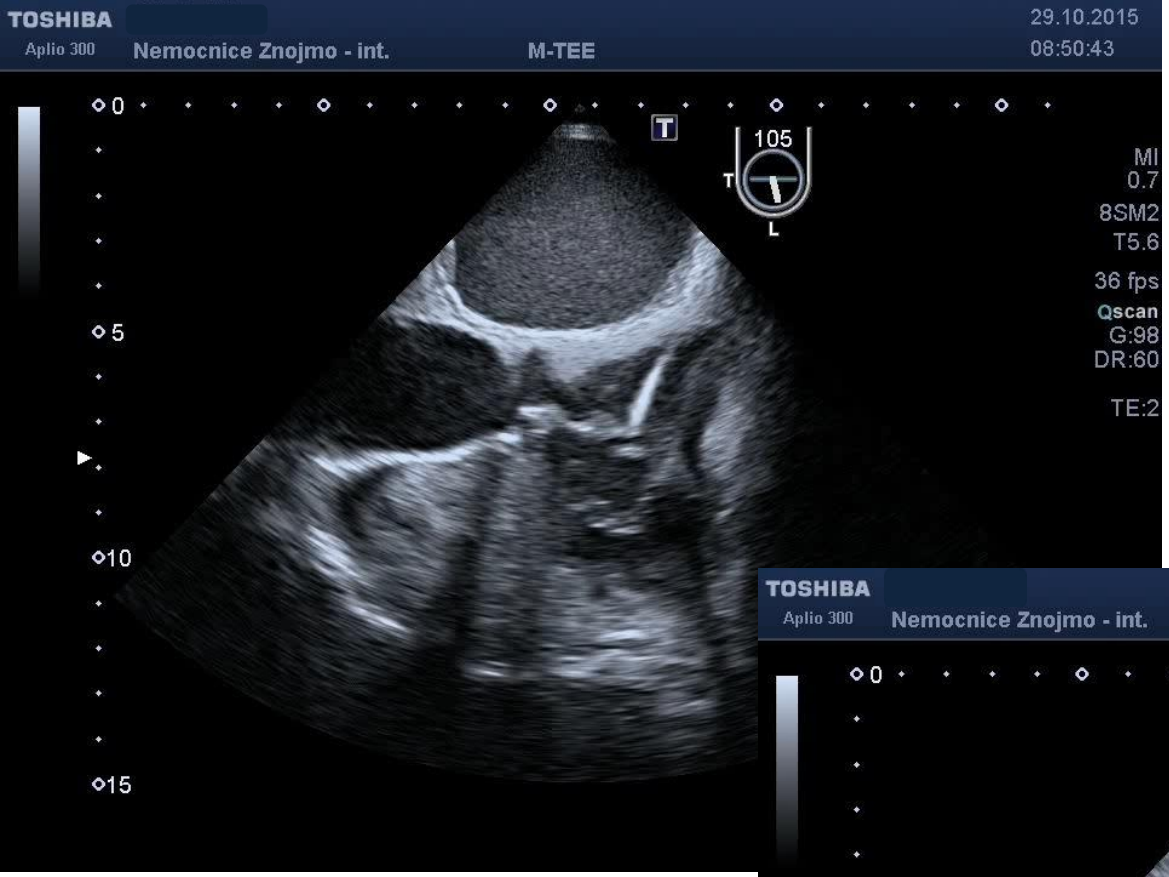


Source of sepsis




TOSHIBA
Aplio 300
Nemocnice Znojmo - int.
M-TEE
13.01.2016
08:27:48
T
61
T
L
MI
0.8
8SM2
T5.6
36 fps
Qscan
G:91
DR:60
TE:2
0
5
10
14


TOSHIBA
Aplio 300
Nemocnice Znojmo - int.
Adult Heart
05.08.2015
18:35:43
T
MI
1.3
5S1
T3.0
43 fps
G:88
DR:60
TE:1
0
5
10
16


TOSHIBA
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Nemocnice Znojmo - int.
M-TEE
29.10.2015
08:50:43
105
MI
0.7
8SM2
T5.6
36 fps
Qscan
G:98
DR:60
TE:2
0
5
10
15


TOSHIBA
Aplio 300
Nemocnice Znojmo - int.
M-TEE
29.10.2015
08:52:53
155
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8SM2
T5.6
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Qscan
G:98
DR:60
TE:2
0
5
10
15


SR
T1W_TSE
SE:401
IM:8
074Y
M
A
1
9
8
P
1
3
6

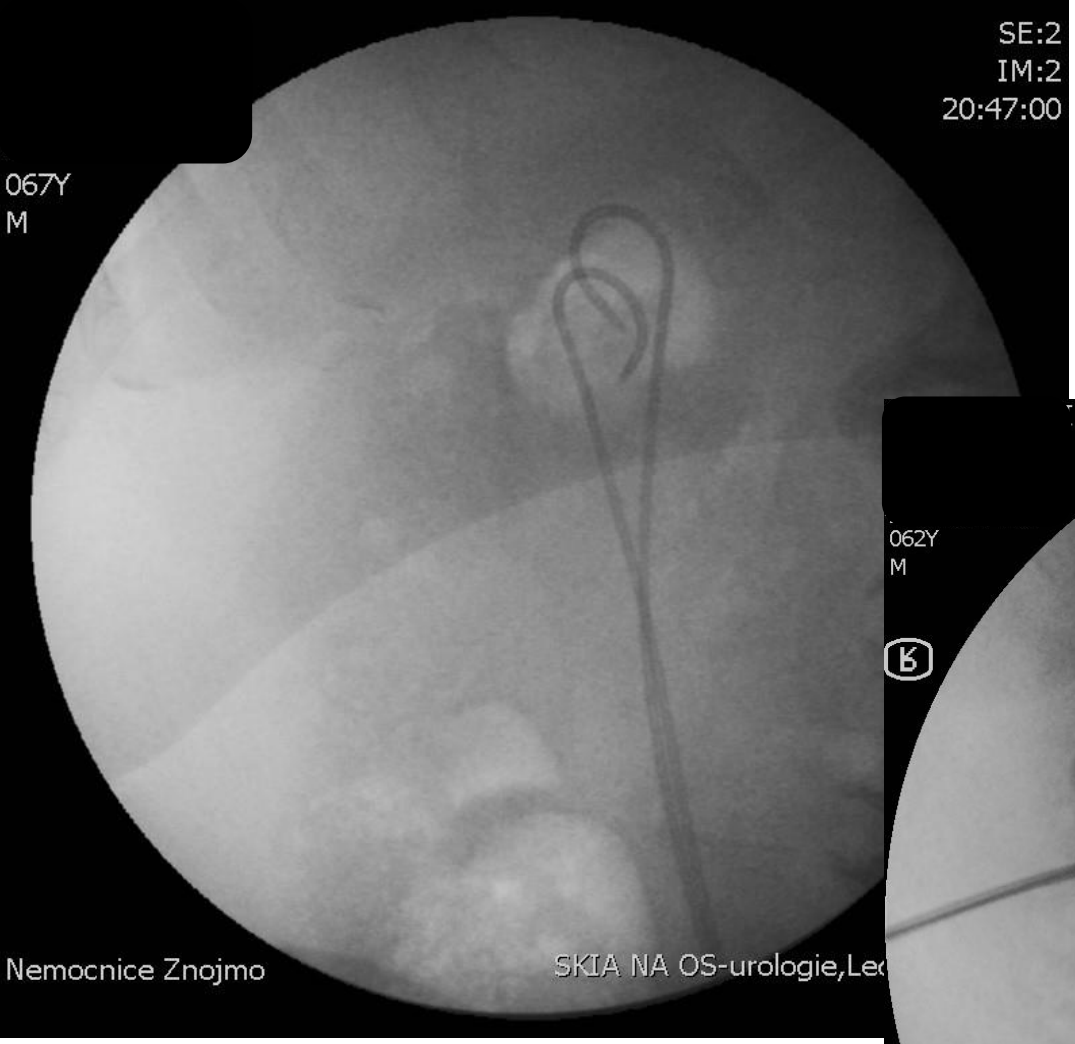

SR
STIR_longTE
SE:501
IM:10
074Y
M
A
1
9
8
P
1
3
6

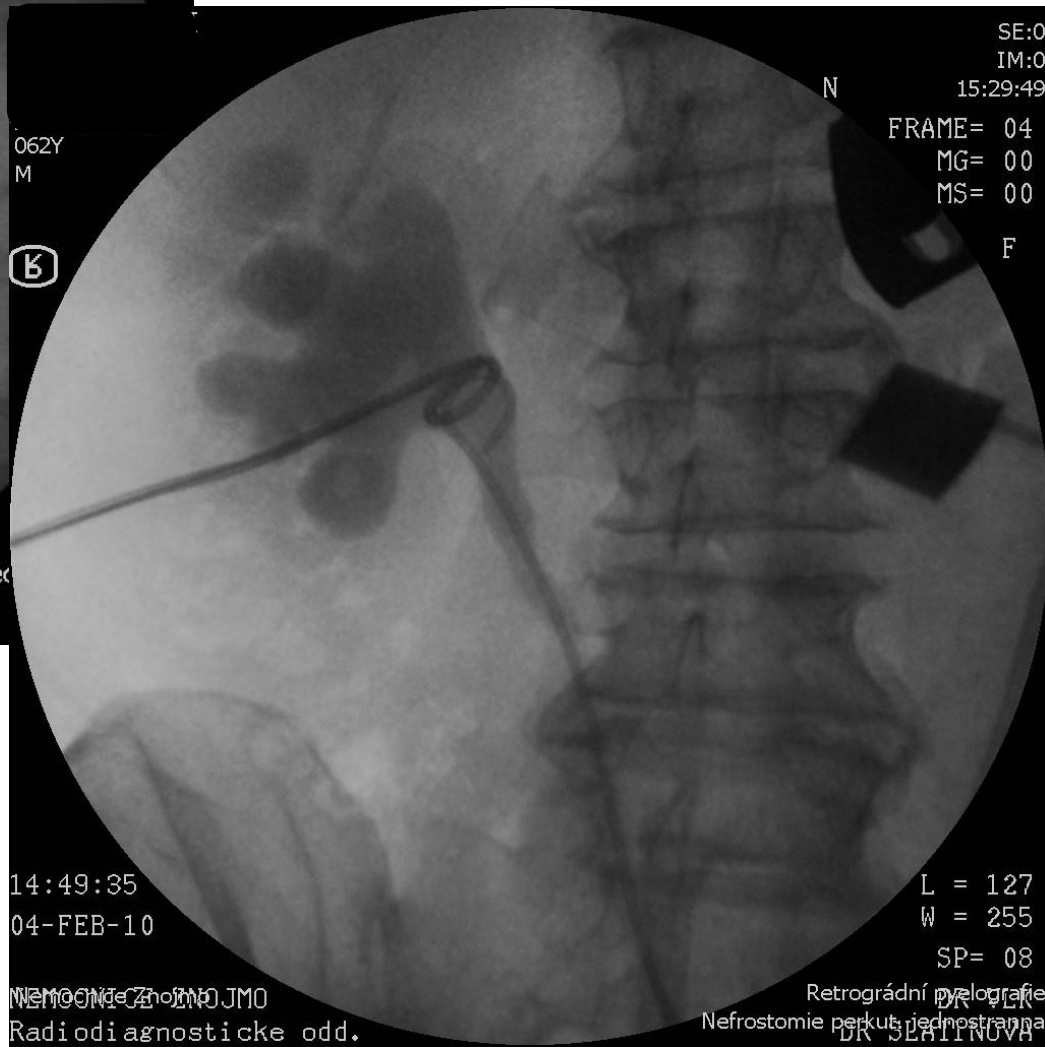

SR
KL_T1W_SPIR 7.5mlGADOVIST
SE:701
IM:6
074Y
M
A
1
9
8
P
1
3
6
Nemocnice Znojmo
06.08.2015
11:30:38
IL
EC:1
DFOV:334
thickness:4
gap:4.4
TE:7.8
TR:400


SR
KL_T1W_SPIR 7.5mlGADOVIST
SE:701
IM:9
074Y
M
A
1
9
8
P
1
3
6
Nemocnice Znojmo
06.08.2015
11:30:38
IL
EC:1
DFOV:334
thickness:4
gap:4.4
TE:7.8
TR:400

Identification and control of septic focus

- prompt **identification** and **treatment** of the primary site of infection are essential
- BC, sputum and urine for Gram stain and culture
- remove vascular access devices
- resolve potential urinary or biliary tract obstruction





Retrográdní pyelografie
Nefrostomie perkut. jednostranná


96kV
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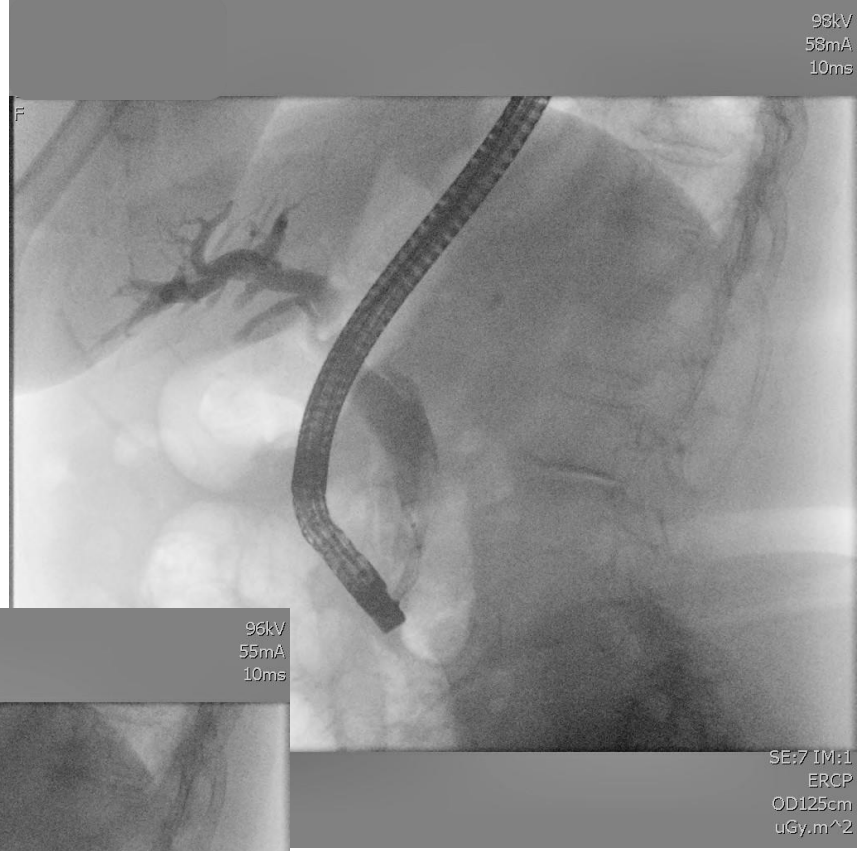
F
12.01.2016
14:27:13
Nemocnice Znojmo p.o.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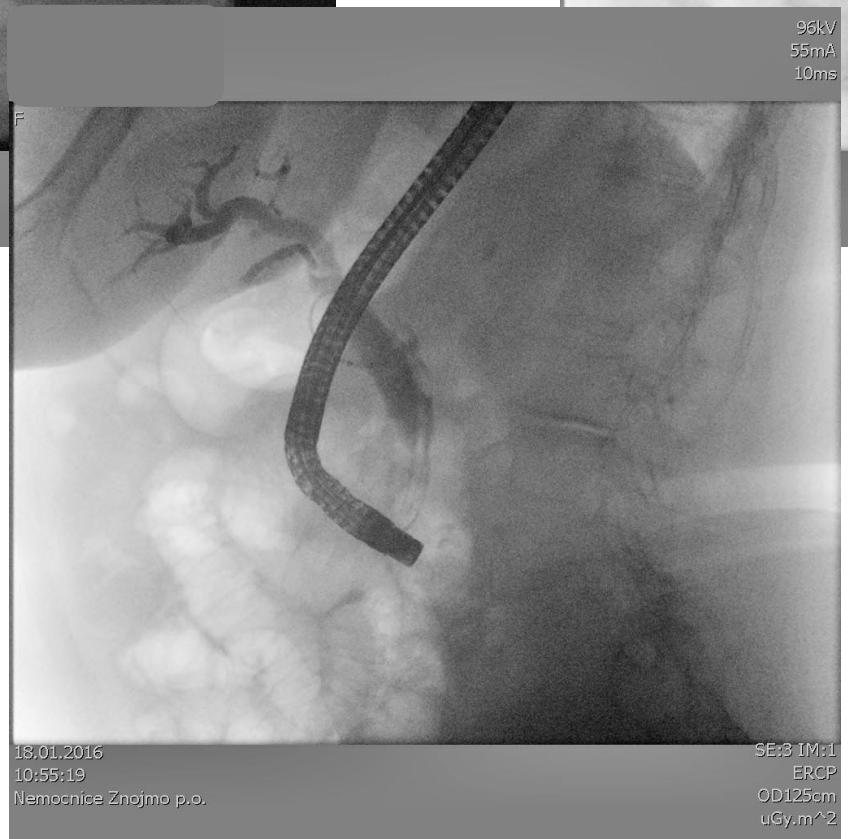
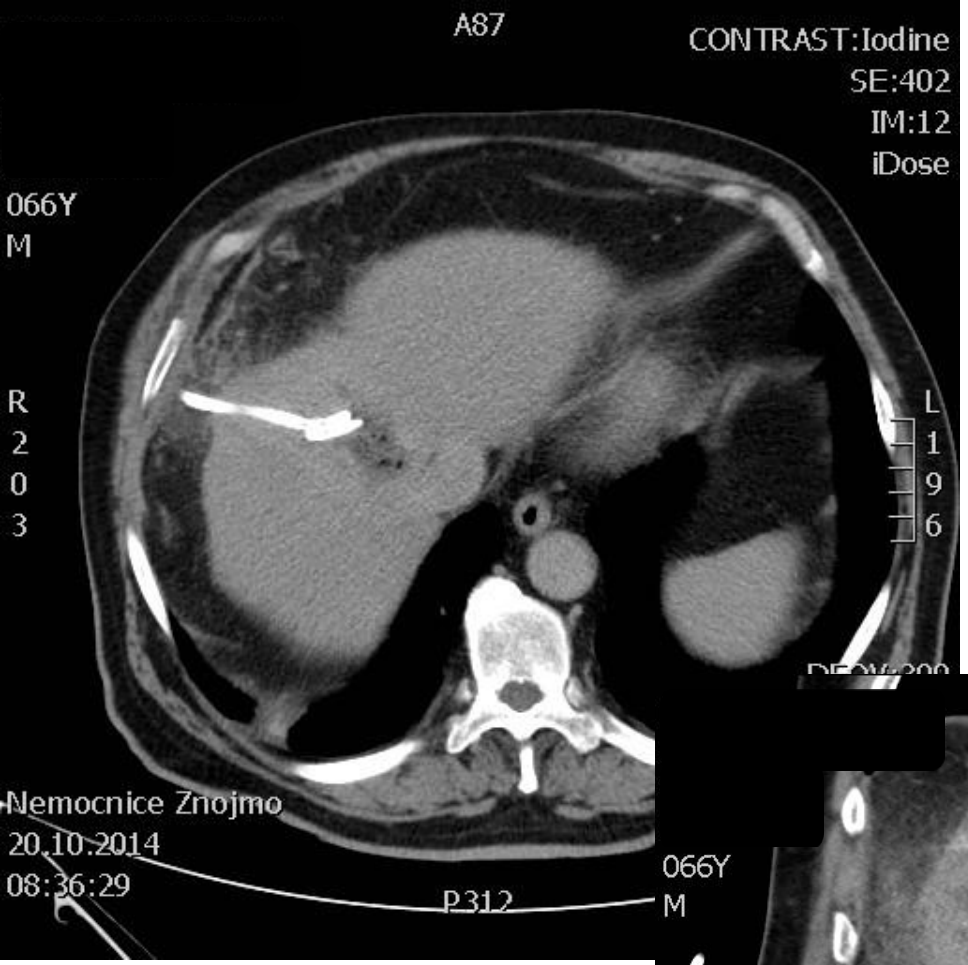
10ms
F
SE:7 IM:1
ERCP
OD125cm
uGy.m^2


96kV
55mA
10ms
F
18.01.2016
10:55:19
Nemocnice Znojmo p.o.
SE:3 IM:1
ERCP
OD125cm
uGy.m^2

Identification and control of septic focus

- prompt identification and treatment of the primary site or sites of infection are essential
- BC, sputum and urine for Gram stain and culture
- remove vascular access devices
- resolve potential urinary or biliary tract obstruction
- abscesses should undergo drainage (percutaneous or surgical)


A87
CONTRAST:Iodine
SE:402
IM:12
iDose
066Y
M
R
2
0
3
L
1
9
6
Nemocnice Znojmo
20.10.2014
08:36:29
P312


S892
CONTRAST:Iodine
SE:403
IM:28
iDose
066Y
M
R
2
0
8
L
1
9
8
DFOV:
TILT:0
:
5 mm
kV:120
mAs:301
mm
Nemocnice Znojmo
20.10.2014
08:36:29
S647

Identification and control of septic focus

- prompt identification and treatment of the primary site or sites of infection are essential
- BC, sputum and urine for Gram stain and culture
- remove vascular access devices
- resolve potential urinary or biliary tract obstruction
- abscesses should undergo drainage (percutaneous or surgical)
- surgeon wanted (abdomen, soft tissue)

Blood glucose control

- hyperglycemia and insulin resistance are common in critically ill patients, independent of a history of diabetes mellitus
- target blood glucose range 6.0 – 10.0 mmol/l
- 2 consecutive values of glucose > 9.9 mmol/l, consider insuline therapy
- reassess glycemia after 1-2 hrs until BG level and insulin dose is stable
- regular check of BG every 4-6 hrs
- hypoglycemia is dangerous !

VISEP

Intensive insulin therapy and pentastarch resuscitation in severe sepsis

N Engl J Med. 2008;358(2):125

1st group - intensive glucose control:

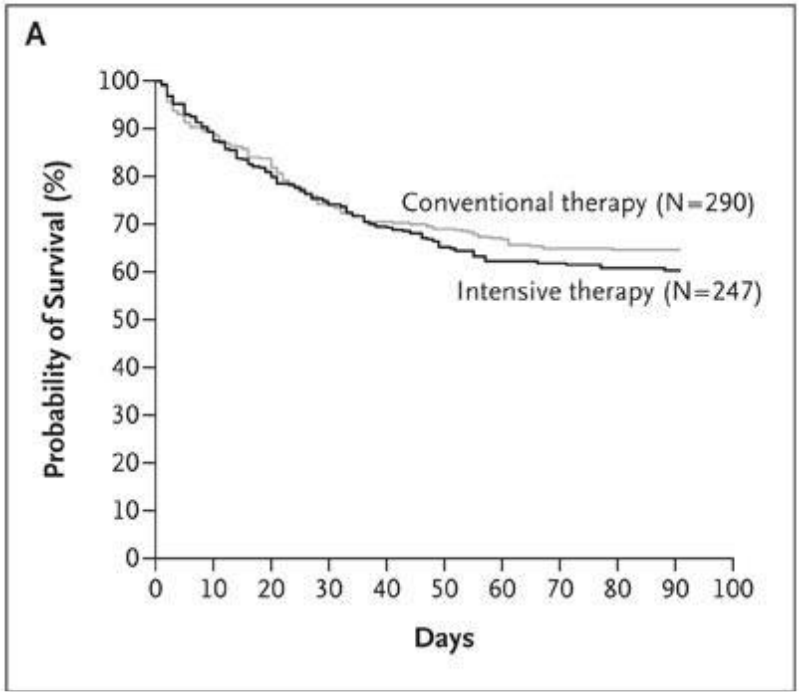
4.4 – 6.1 mmol/l

2nd group - conventional glucose control:

10.0 – 11.1 mmol/l

incidence of severe hypoglycemia

17.0 vs. 4.1 % $p<0.0001$



NICE - SUGAR

Intensive versus Conventional Glucose Control in Critically Ill Patients
N Engl J Med 2009;360:1283-97

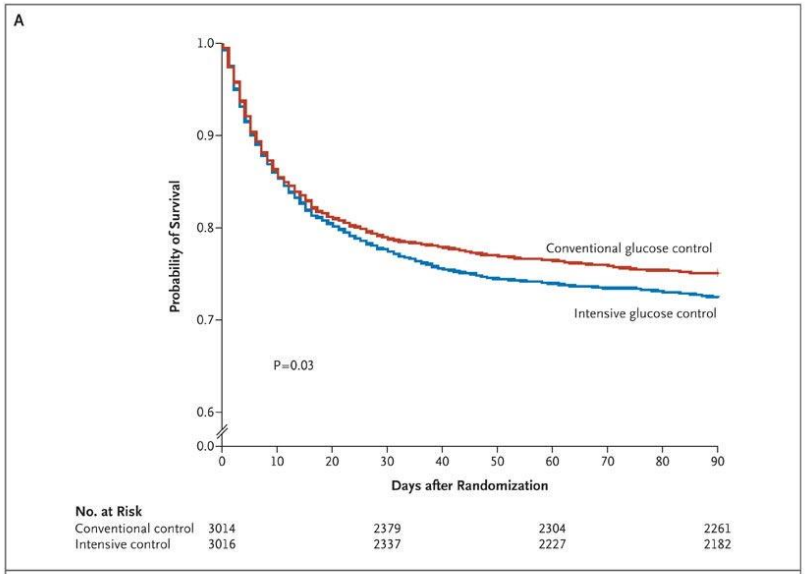
1st group - intensive glucose control: 4.5 – 6.0 mmol/l

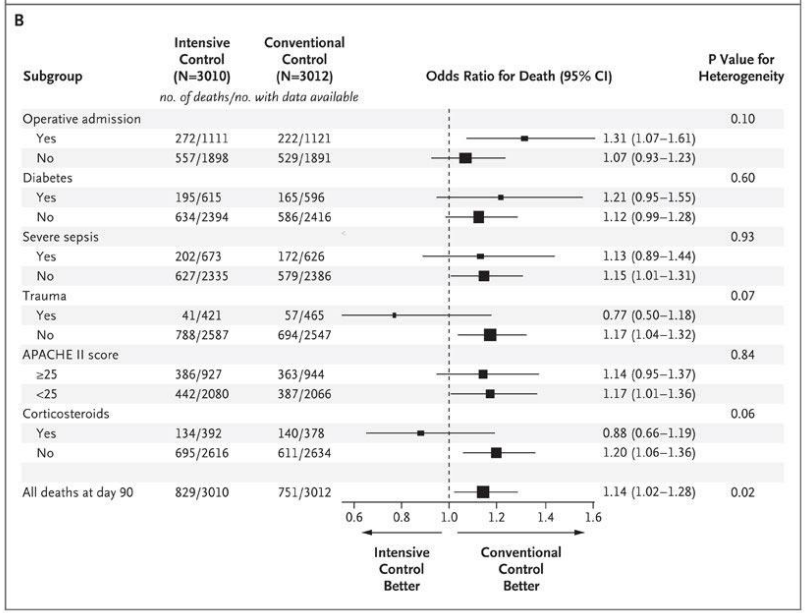
2nd group - conventional glucose control: < 10.0 mmol/l

incidence of severe hypoglycemia

6.8 vs. 0.5 % p<0.001

↑ mortality in intensive glucose control group





Nutrition in severe sepsis

- start within 48 hrs from admission
- enteral nutrition rather than parenteral
- low-dose EN for the first week < 500 kcal/day (EDEN trial → Surviving Sepsis Campaign guidelines)
- close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients (Crit Care. 2014)
- immunonutrition not recommended
- no proof for glutamine and antioxidants

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

REducing Deaths due to OXidative Stress (The REDOXS Study): N Engl J Med 2013

Table 3. Clinical Outcomes in All 1218 Study Patients.

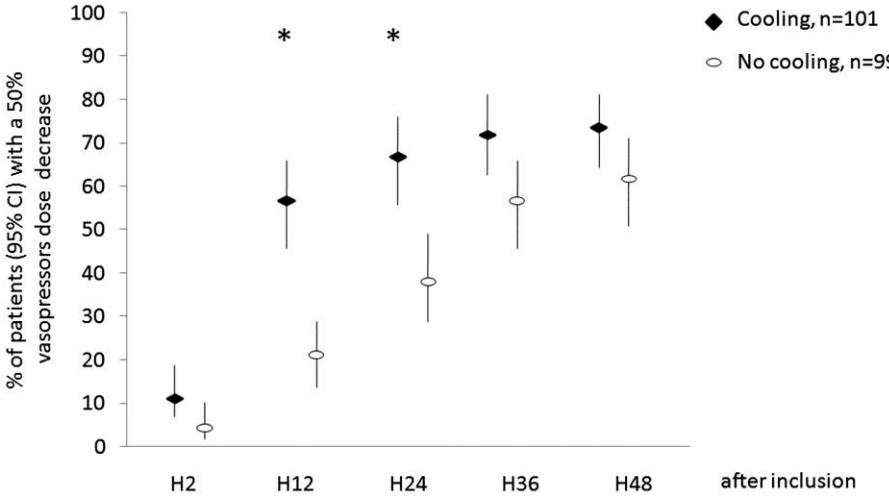
Variable	Glutamine	No Glutamine	P Value	Antioxidants	No Antioxidants	P Value
Death — no. of patients/total no. (%)						
At day 28	198/611 (32.4)	165/607 (27.2)	0.05*	190/617 (30.8)	173/601 (28.8)	0.48
At day 14	157/611 (25.7)	129/607 (21.3)	0.07	154/617 (25.0)	132/601 (22.0)	0.23
In hospital	227/611 (37.2)	188/607 (31.0)	0.02	216/617 (35.0)	199/601 (33.1)	0.51
At 6 mo†	259 (43.7)	218 (37.2)	0.02	242 (40.4)	235 (40.6)	0.87
Time from randomization to final discontinuation of mechanical ventilation and alive — days‡						
Median	11.0	8.7	0.03	9.1	10.5	0.67
Interquartile range	4.0–undefined	3.9–58.8		3.9–undefined	4.0–undefined	
Time from randomization to discharge alive from ICU — days‡						
Median	17.1	13.1	0.03	15.1	14.0	0.34
Interquartile range	7.3–undefined	7.1–undefined		7.2–undefined	7.2–undefined	
Time from randomization to discharge alive from hospital — days‡						
Median	51.0	40.1	0.04	43.8	42.7	0.39
Interquartile range	17.9–undefined	16.3–undefined		18.0–undefined	16.2–undefined	
Hospital length of stay — days§						
Median	16.0	17.1	0.15	16.9	16.6	0.97
Interquartile range	7.9–33.9	8.4–36.1		8.0–36.2	8.1–33.0	
ICU length of stay — days§						
Median	8.4	8.9	0.62	8.4	8.9	0.87
Interquartile range	4.4–16.0	5.1–15.3		4.6–15.3	5.1–15.8	
Time from randomization to final discontinuation of mechanical ventilation — days§						
Median	6.1	5.9	0.71	6.0	6.1	0.69
Interquartile range	2.8–12.8	2.9–11.9		2.8–11.8	2.9–12.7	

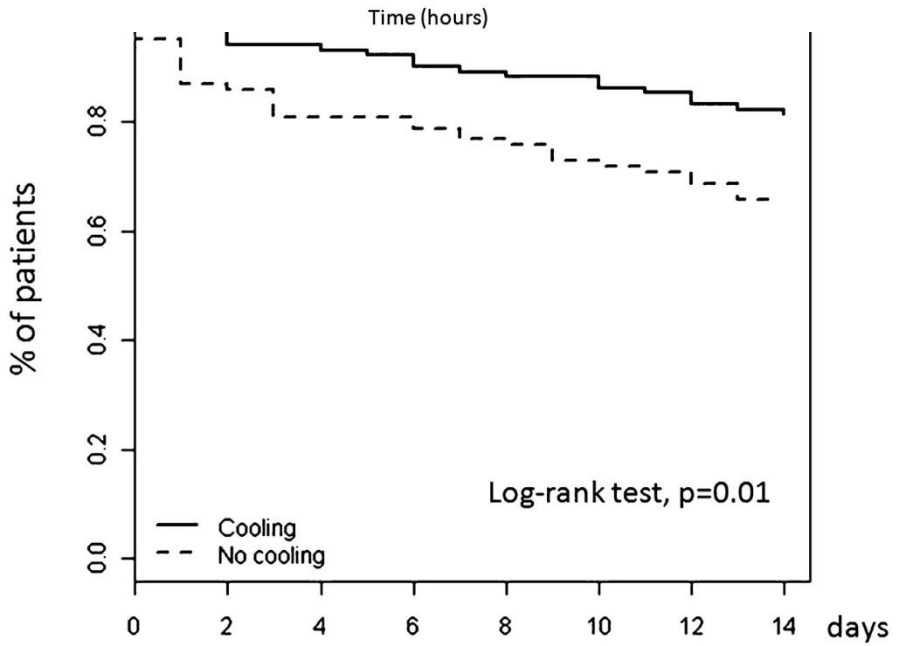
External cooling

- controlling fever during severe sepsis and septic shock has potential benefits and adverse effects
- external cooling - core body temperature of 36.5 to 37°C for 48 hrs

Fever Control Using External Cooling in Septic Shock
Am J Respir Crit Care Med 2012; Vol 185, Iss. 10, pp 1088–1095

- 1st group: > 38.3 ˚C
- 2nd group: 36.5 – 37 ˚C





Ineffective or unproven therapies for sepsis

- polyclonal immunoglobulins do not significantly reduce mortality in adults with severe sepsis – not recommended
- naloxon, pentoxyfilin, statin
- hemofiltration
- bicarbonate therapy in case of lactate acidosis pH > 7.15
- rhAPC, G-CSF


Thank you for your attention