Fluids in Sepsis: How much and what type?

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In critically ill patients: too little fluid…

- Low preload, low cardiac output, low blood pressure, low perfusion
- Arrhythmia (hypovolemia)
- GI dysfunction (hypoperfusion)
  - Postoperative ileus, PONV
  - Upper GI bleeding
  - Anastomotic leak
- Infectious complication (tissue hypoperfusion)
- Acute renal insufficiency or failure (decreased renal blood flow)

2002; 89: 622-632.

In critically ill patients: too much fluid…

- Pulmonary edema, prolonged mechanical ventilation
- GI dysfunction
  - Abdominal compartment syndrome
  - Ileus
  - Anastomotic leak
- Hemodilution and coagulopathy

Fluids in sepsis

- Goals?
- What type of fluid?
  - Past
  - Present
  - Future
- How much fluid?
  - what if I give too much?
  - when to stop: clinical signs, biomarkers, imaging?

Sepsis / Severe sepsis / ***Septic shock***

Severe sepsis: Sepsis plus evidence of organ dysfunction

- Arterial hypoxemia ($PaO_2/FiO_2<300$)
- Acute oliguria (urine output <0.5 mL/kg per hour for at least 2 h despite adequate fluid resuscitation
- Increase in creatinine >0.5 mg/dL
- Coagulation abnormalities (INR>1.5, aPTT>60 s, platelets <100,000/mL)
- Hepatic dysfunction (elevated bilirubin)
- Paralytic ileus
- Decreased capillary refill or skin mottling

Septic shock: Sepsis with hypotension refractory to fluid resuscitation or hyperlactatemia.

- Refractory hypotension persists despite resus. with IV fluid bolus of 30 mL/kg
- Hyperlactatemia >2 mmol/L

Sepsis / Severe sepsis / Septic shock

- Obstructive
- Hypovolemic
- **Cardiogenic**
- **Distributive**

Septic *shock*

- Shock: lack of oxygenated hemoglobin being delivered to tissues

Septic *shock*

- Shock: lack of oxygenated hemoglobin being delivered to tissues

- **FLOW** (not blood pressure)

Not blood pressure, but FLOW…

However, for organs to be perfused, certain critical perfusion pressures must be present:

- **Brain**: MAP of 50 (non-vasculopath dogs, Plöchl et al. 1998)
- **Heart**: MAP of 65 (Dunser et al.)
- **Kidneys**: MAP of 65-75? (Bellomo, Wan, and May 2008)

What type of fluid should I give in sepsis?

- 1996:

  "Blood volume expansion with crystalloid, colloid, and red cell concentrate"

Sepsis… recognition and treatment…

- Important…
- then in 2001

Everything changed in 2001…

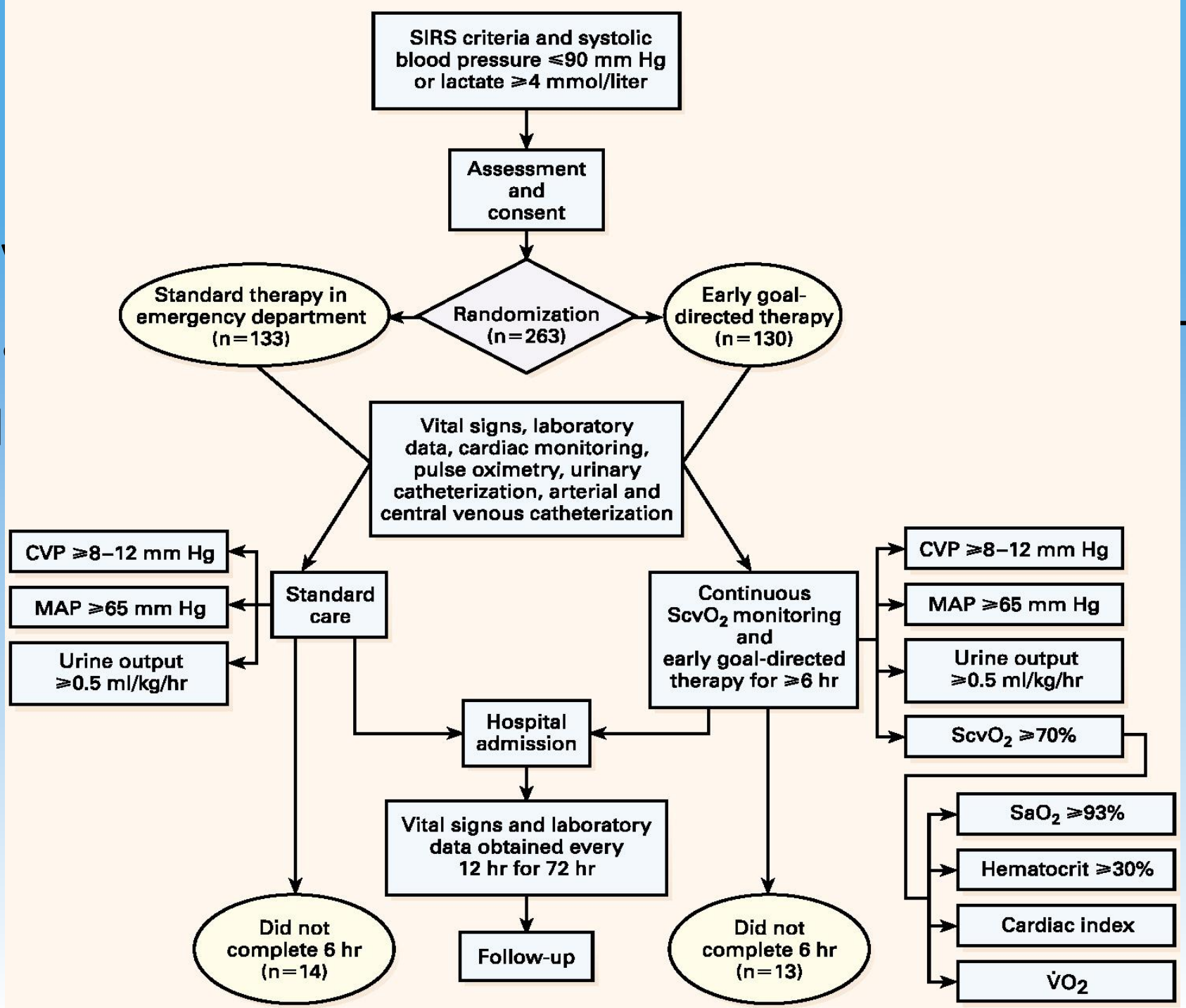
Rivers, et al. in NEJM (industry bias? single center)

Standard care vs early goal-directed therapy (EGDT)

Mortality: 46.5% vs 30.5%

The New England Journal of Medicine

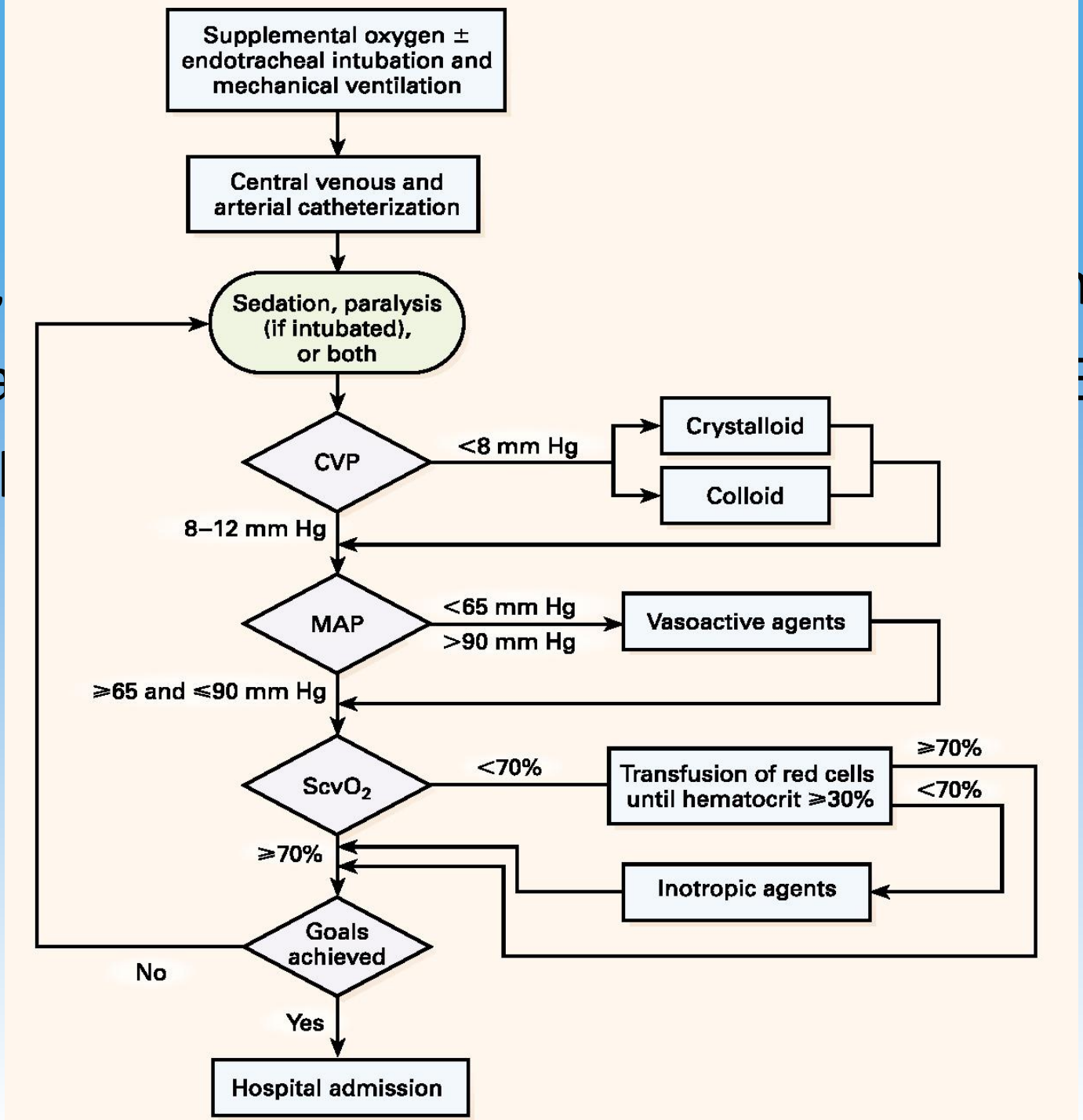
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK


SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter
Assessment and consent
Randomization (n=263)
Standard therapy in emergency department (n=133)
Early goal-directed therapy (n=130)
Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
Standard care
Continuous $ScvO_2$ monitoring and early goal-directed therapy for ≥6 hr
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
$ScvO_2$ ≥70%
SaO_2 ≥93%
Hematocrit ≥30%
Cardiac index
$\dot{V}O_2$
Hospital admission
Vital signs and laboratory data obtained every 12 hr for 72 hr
Follow-up
Did not complete 6 hr (n=14)
Did not complete 6 hr (n=13)

Rivers, ...ter)

Standa... EGDT)

Mortal...



EGDT saves lives

Early… first 30 minutes

Goal-directed… CVP, MAP, S_{cvO2}, HCT

Treatment… crystalloid (RBCs if needed)

Mortality: 46.5% vs 30.5%

Quick recognition and treatment of septic patients

- recognition

- oxygen
- fluids – which one?
- pressors?
- monitoring

Recent studies regarding sepsis resuscitation

All published in the New England Journal of Medicine

ProCESS, ARISE, ProMISe

ProCESS Investigators, Yealy DM, Kellum JA, Juang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370(18):1683-1693

The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014; 371:1496-1506

Mouncey PR, Osborn TM, Power GS, et al for the ProMISe trial investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015: DOI: 10.1056/NEJMoa1500896

Fluids in sepsis: ProCESS

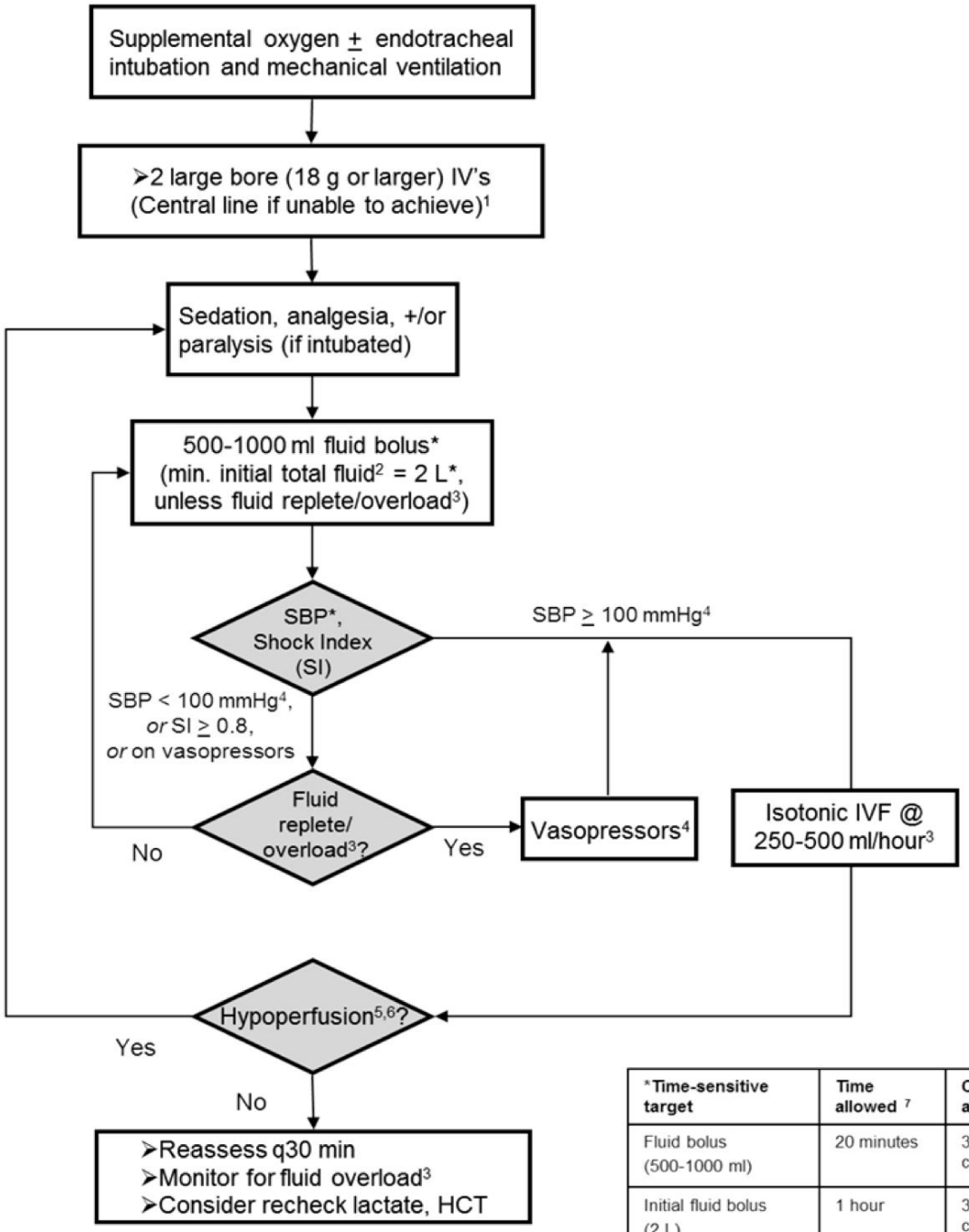
- 2014, NEJM, randomized, multicenter
- **Three** groups: EGDT, “standard protocol”, “usual care”, 1:1:1
- 1,351 patients

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

In a multicenter trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes.

Flui

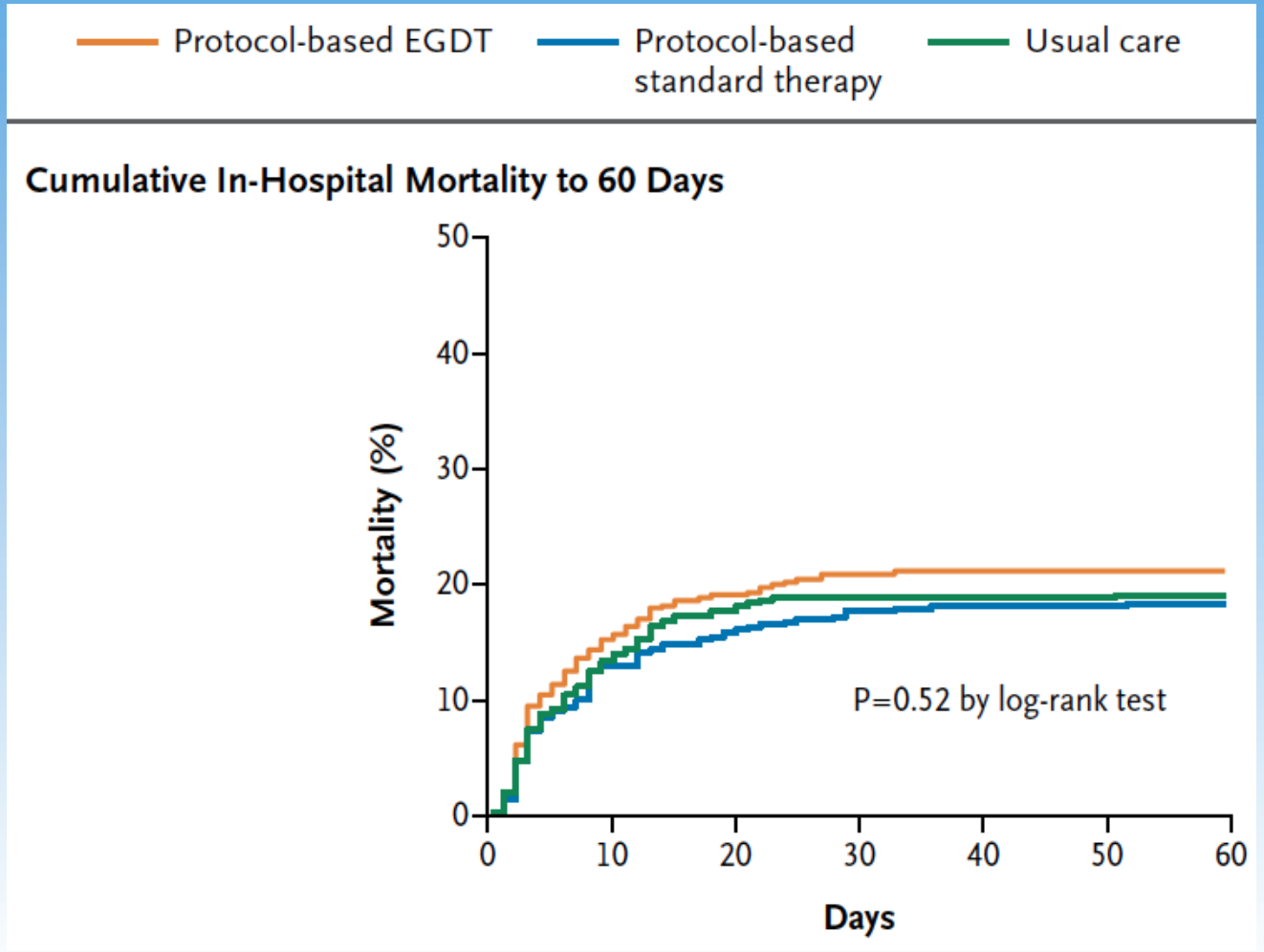
Standard treatment protocol:



*Time-sensitive target	Time allowed [7]	Corrective action
Fluid bolus (500-1000 ml)	20 minutes	3rd IV or central line
Initial fluid bolus (2 L)	1 hour	3rd IV or central line
SBP ≥ 100 mmHg	1 hour	Vasopressors

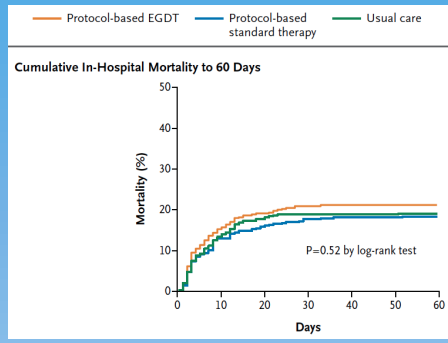
Fluids in sepsis: ProCESS

- Primary outcome: mortality at 60 days



Fluids in sepsis: ProCESS

- Primary outcome: mortality at 60 days



The ProCESS Trial — A New Era of Sepsis Management

Craig M. Lilly, M.D.

The importance of early detection and treatment for reducing the mortality associated with sepsis has been a tenet of medical training since the middle ages, when it was noted that ". . . the creased mortality to delays in the administration of appropriate antibiotics[6] suggested that early administration of antibiotics increased survival in all groups of the trial. Indeed, in the ProCESS

Fluids in sepsis: ARISE

- 2014, NEJM, randomized, multicenter
- EGDT vs 'usual care' (in u.c. group, no $ScvO_2$ measurement allowed in first 6 hours)
- mortality at 90 days
- 1,600 patients

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

In critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days.

Fluids in sepsis: ARISE

Measure	EGDT	Usual Care	AD	95% CI	p
90-day mortality Mean (SD)	18.6%	18.8%	-0.3%	-4.1 to 3.6%	0.90

AD = absolute difference; CI = confidence intervals; p = p value

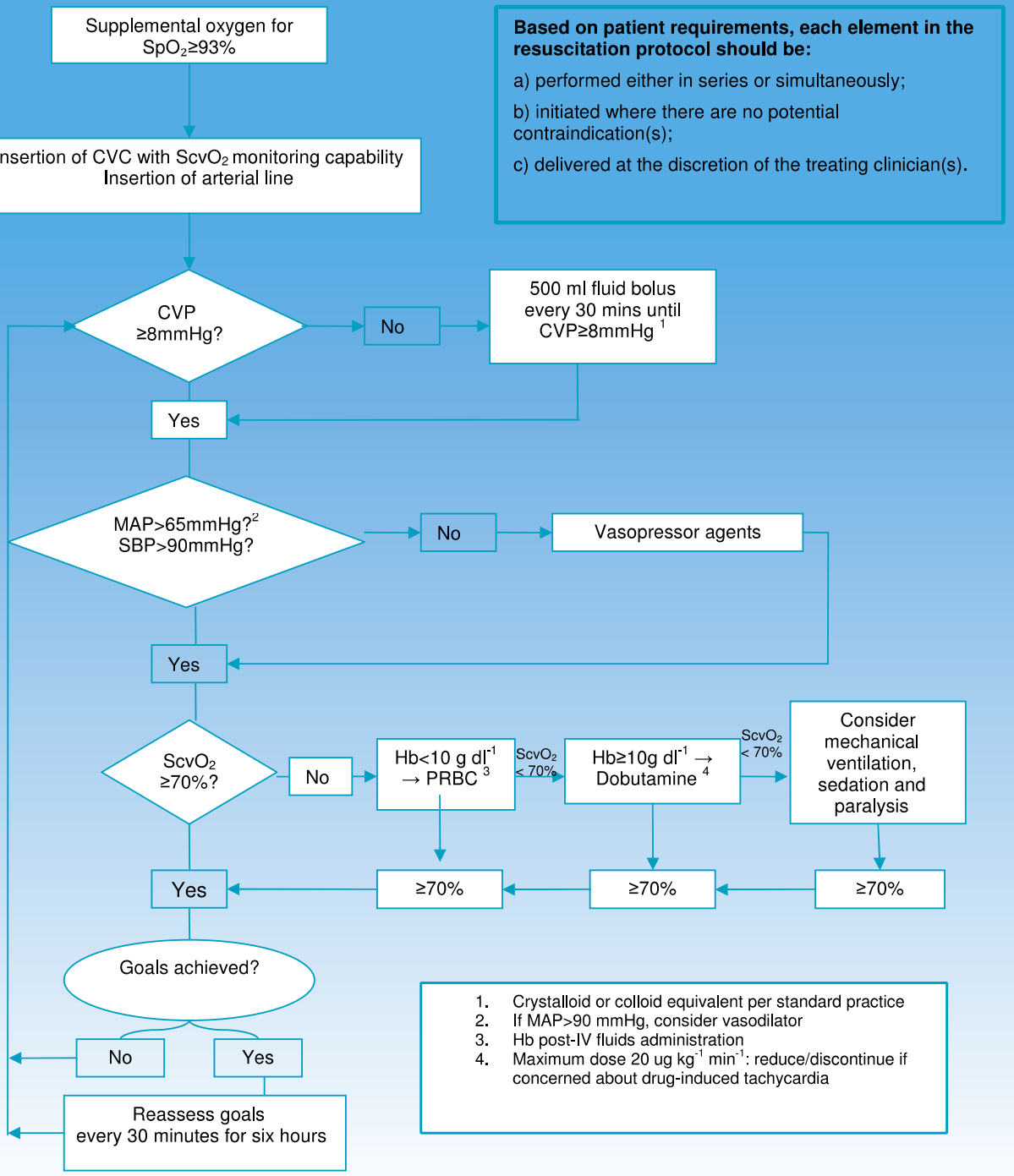
Secondary Outcomes

Measure	EGDT	Usual Care	RR	95% CI	p
Vasopressor support	76.3%	65.8%	1.16	1.09 to 1.24	< 0.001
ED LOS hours	1.4	2.0		n/a	< 0.001
ICU LOS days	2.8	2.8		n/a	0.81
Hospital LOS days	8.2	8.5		n/a	0.89
28-day mortality	14.8%	15.9%	0.93	0.73 to 1.17	0.53

Usual care or 6-hour protocol: ProMISe

- 2015, England, randomized
- Assumed 40% mortality at 90 days
- EGDT with central catheter for 6 hours vs ‘standard care’
- 1,260 patients

Trial of Early, Goal-Directed Resuscitation for Septic Shock


Supplemental oxygen for SpO_2≥93%
Insertion of CVC with $ScvO_2$ monitoring capability
Insertion of arterial line
CVP ≥8mmHg?
No
500 ml fluid bolus every 30 mins until CVP≥8mmHg [1]
Yes
MAP>65mmHg?[2] SBP>90mmHg?
No
Vasopressor agents
Yes
$ScvO_2$ ≥70%?
No
Hb<10 g dl^{-1} → PRBC [3]
$ScvO_2$ < 70%
Hb≥10g dl^{-1} → Dobutamine [4]
$ScvO_2$ < 70%
Consider mechanical ventilation, sedation and paralysis
Yes
≥70%
≥70%
≥70%
Goals achieved?
No
Yes
Reassess goals every 30 minutes for six hours
Based on patient requirements, each element in the resuscitation protocol should be:
a) performed either in series or simultaneously;
b) initiated where there are no potential contraindication(s);
c) delivered at the discretion of the treating clinician(s).
1. Crystalloid or colloid equivalent per standard practice
2. If MAP>90 mmHg, consider vasodilator
3. Hb post-IV fluids administration
4. Maximum dose 20 ug kg^{-1} min^{-1}: reduce/discontinue if concerned about drug-induced tachycardia

Usual care or 6-hour protocol: ProMISe

All cause mortality at 90 days: EGDT vs. usual care

29.5% vs. 29.2% p=0.9

Secondary outcomes: **SOFA at 6 hours**: 6.4 vs. 5.6

SOFA at 72 hours: 4.0 vs. 3.7

Requirement for, and duration of, critical care unit organ support: no difference in receipt or days free (up to 28 days) from advanced respiratory, advanced cardiovascular support or renal support

Comparison of recent EGDT studies

	Rivers et al	ProMISe	ProCESS	ARISE
Location	US	UK	US	Australasia
Population	263	1260	1351	1600
APACHE II (approx)	20	18	21	15
Sepsis Definition				
Suspected / Actual Infection	Yes	Yes	Yes	Yes
SIRS criteria ≥ 2	Yes	Yes	Yes	Yes
Refractory ↓BP or lactate > 4 mmol/l	Yes	Yes	Yes	Yes
Protocol				
Fluid before randomisation	20–30 ml/kg	> 1000 ml	~20–30 ml/kg Changed during study	> 1000 ml
Recruitment	not specified	<6h from ED arrival & <2h from shock criteria	<12h from ED arrival & <2h from shock criteria	<6h from ED arrival & <2h from shock criteria
Intervention	EGDT 6 hours	EGDT 6 hours	EGDT 6 hours	EGDT 6 hours
Control	Usual therapy	Usual therapy	1) Protocol usual therapy 2) Usual therapy	Usual therapy
Primary outcome	In-hospital mortality	90-day mortality	60-day mortality	90-day mortality
Primary Outcome				
Intervention	30.5%	29.5%	21.0%	18.6%
Control	46.5%	29.2%	1) 18.2% 2) 18.9%	18.8%

Goals: high or low mean arterial pressure?

- 2014, randomized
- Mean arterial pressure of 80-85 vs 65-70 mmHg
- Mortality at 28 days: 36.6% vs 34.0%
- Mortality at 90 days: 43.8% vs 42.3%

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

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days.

Crystalloids vs colloids in sepsis

- Albumin
- Hydroxyethyl starch solutions

Fluids in sepsis: albumin

- 2004, randomized, multiple ICU, double-blind
- crystalloid or 4% albumin
- No differences in…
  - days in ICU, days on ventilator, days on dialysis
  - deaths at 28 days
  - single organ failure
  - multiple organ failure

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

Fluids in sepsis: albumin

- 2014, randomized, Italy, multicenter
- crystalloid or cystalloid + 20% albumin
- Death at 28 days: 32.0% vs 31.8%
- Death at 90 days: 43.6% vs 41.1%

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Fluids in sepsis: starches

- 2012, randomized, ICU
- Normal saline or 6% hydroxyethyl starch for all fluid resuscitation
- At 90 days, no difference in death overall or in any subgroup

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

Fluids in sepsis: red blood cell transfusion?

- delivery of oxygenated hemoglobin to tissues

Red blood cell transfusion?

- Shock: lack of ***oxygenated hemoglobin*** being delivered to tissues

But, blood transfusions = increase in infections

Fluids in sepsis: red blood cell transfusion?

- delivery of oxygenated hemoglobin to tissues
- TRISS
- 2014, multicenter, ICU, randomized
- RBCs given if Hgb < 9 gm/dL ***or*** <7 gm/dL
- death at 90 days 45.0% vs 43.0%

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Fluid resuscitation in sepsis: conclusion

- ~~RBCs~~
- ~~starches~~
- ~~albumin~~
- crystalloid…

Crystalloids

mmol/L	Na	K	Ca	Cl	osmolality	pH
Normal saline	154	0	0	154	310	5.5
Ringer's lactate	130	4	2.7	109	273	6.5
Isolyte®	140	5	2.5	103	295	6.7

Crystalloids

mmol/L	Na	K	Ca	**Cl**	osmolality	pH
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Crystalloids in Turkey: 1 liter costs…

- Normal saline: 1.45 TL
- Lactated Ringer's: 1.93 TL
- Isolyte®: 2.13 TL

IV fluids *and* noradrenalin

Noradrenalin vasoconstricts = increases afterload

IV fluids *and* noradrenalin

Noradrenalin vasoconstricts = increases afterload, ***and it increases venous return***

- Crit Care Med. 2012;40:3146-3153
- Crit Care Med. 2011;39:689-94
- Crit Care Med. 2013;41:143-50
- Critical Care 2007;11(Suppl 2):P37
- Critical Care 2010, 14:R142
- Anesthesiology 2014; 120:365–77

How can a vasopressor help?

- Achieve critical perfusion pressures (heart will get better, but may look worse initially)
- Increase venous return
- Avoid gut ischemia and flow reduction

Not blood pressure, but FLOW…

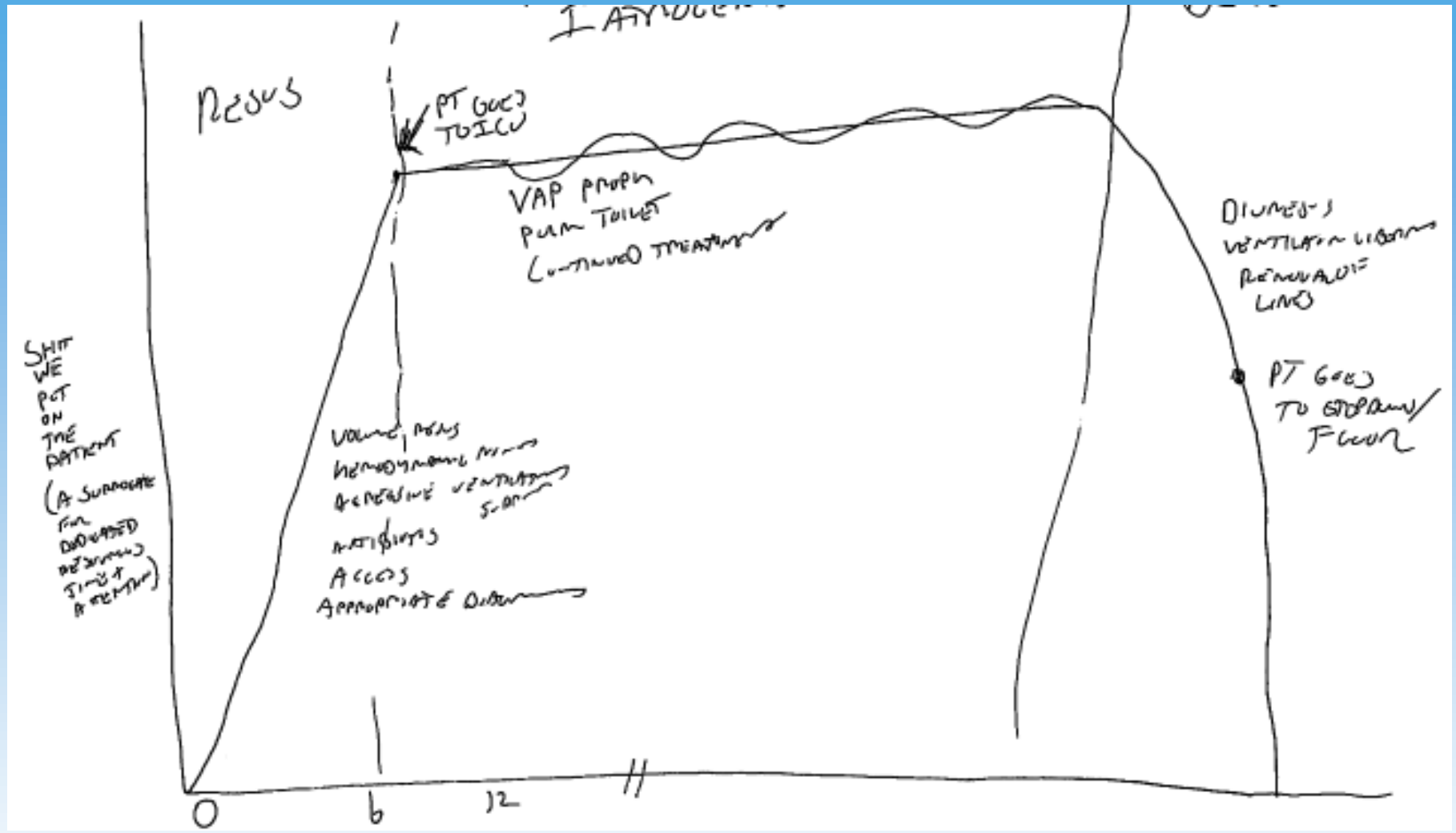
However, for organs to be perfused, certain critical perfusion pressures must be present:

- **Brain**: MAP of 50 (non-vasculopath dogs, Plöchl et al. 1998)
- **Heart**: MAP of 65 (Dunser et al.)
- **Kidneys**: MAP of 65-75? (Bellomo, Wan, and May 2008)

Fluid resuscitation in sepsis: conclusion

- ~~RBCs~~
- ~~starches~~
- ~~albumin~~
- crystalloid… balanced solution (LR or Isolyte® or …)

“Slope of resuscitation” from EMCrit.org



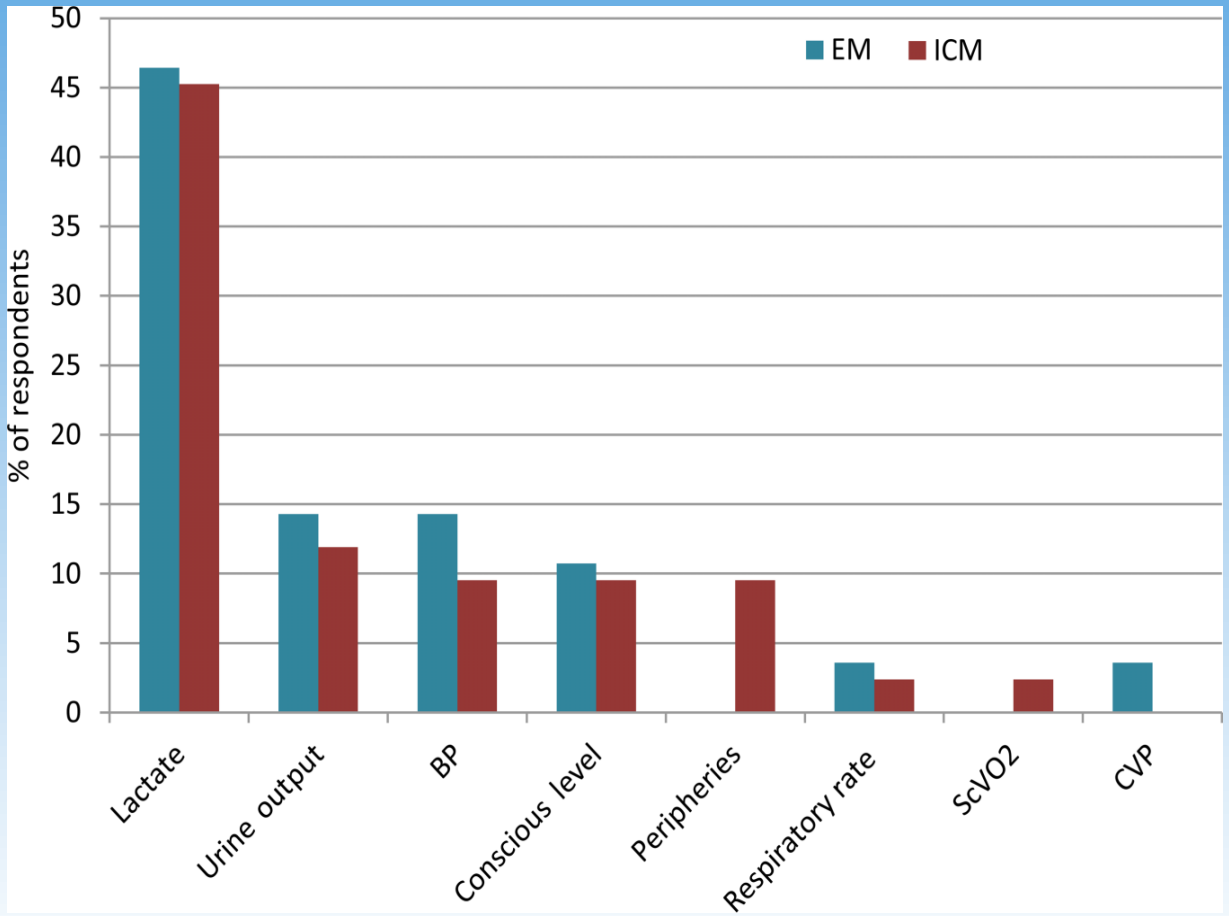
Management of sepsis patients

- 2013, Scotland, questionnaire
- emerg med and internal med (ICU) physicians

Emergency department management of early sepsis: a national survey of emergency medicine and intensive care consultants

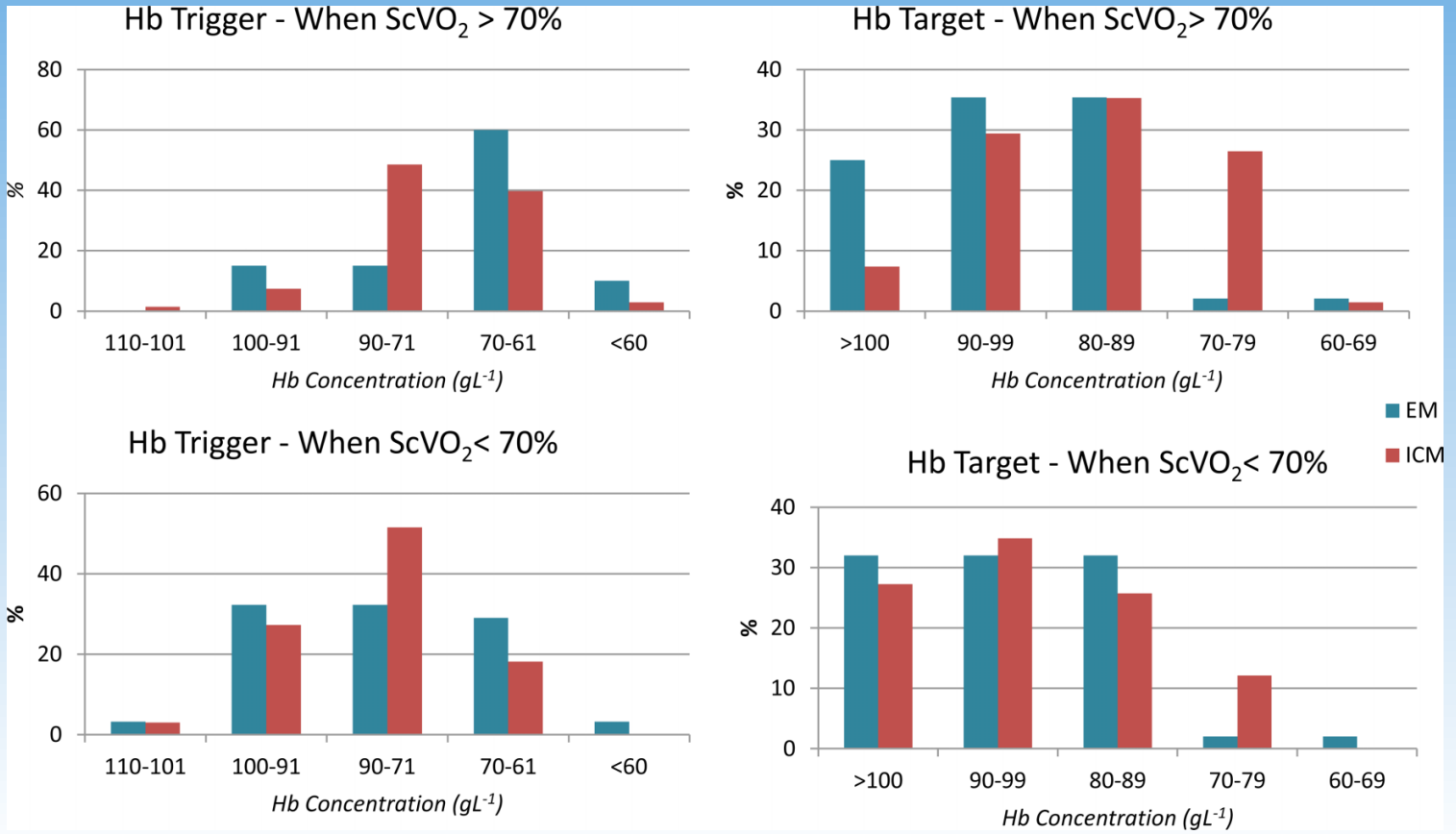
Management of sepsis patients

- 2013, Scotland, questionnaire
- emerg med and internal med physicians
- Regarding adequacy of resuscitation:



Management of sepsis patients

- 2013, Scotland, EM and IM docs
- Trigger for RBC transfusion:



Endpoints

- level of conciousness
- urine output
- shock index
- Arterial-venous CO_2 difference
- $ScvO_2$
- Echo:
  - cardiac output
  - stroke volume
  - IVC collapse

What we need to do

- If hypotensive or lactate >4 mmol/L…
- Within 30 minutes… (measure lactate)
  - oxygenate
  - 2 large-bore IVs, pressure bags, 30 mL/kg crystalloid bolus (balanced solution)
  - cultures/antibiotics

Summary

- MAP of 65 mmHg
- Hemoglobin > 7 gm/dL
- Balanced electrolyte (crystalloid) solution
- An initial dose of 30 mL/kg… then **monitoring** to guide further **therapy**
  - ultrasound, lactate, ven-art CO_2, urine output, PLR
  - more fluids?, noradrenalin?, dobutamine? vasopressin?

Questions? Comments?

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