Fluids in Sepsis

Less is more

Dr Anand Senthi
Joondalup Health Campus ED
MBBS, MAppFin, GradCertPubHlth, FRACGP
@drsenthi

Summary

- Discussion of the evidence for/against fluid resuscitation in septic shock

- What's the alternative to aggressive fluid resuscitation?

Disclosures

- I AM NOT AN EXPERT!
- I have no financial conflicts to disclose

Evidence of benefit of fluid resuscitation

Carcillo, JAMA 1991

- Observational analysis of 34 kids with septic shock who had pulmonary artery catheters placed divided into 3 groups based on fluid in 1st hour:
  - Group 1 <20ml/kg: 6/14 survived
  - Group 2: 20-40ml/kg: 4/11 survived
  - Group 3: >40ml/kg: 8/9 survived

Carcillo, JAMA 1991

- Issues:
  - 1. **Tiny** retrospective study
  - 2. Only patients with pulmonary artery cath included
  - 3. Not controlled for different use of pressors/vent
  - 4. No dose response

EGDT, Rivers 2001

- The primary source of the Surviving Sepsis Guidelines (SSG) on fluid resus
  - EGDT 5 L v Standard care 3.5L in 1st 6 hours
- High controversial – questionable validity
  - Financial conflicts (Rivers and SSG), high mortality, differential clinical expertise
- Questions regarding whether results were real
  - 25 patients excluded post randomisation – if included → no significant mortality reduction
- PROCESS and ARISE now have debunked EGDT

Anecdotal experience

- *We give fluids and patients look better!*

Evidence of Fluid Causing Harms

- Several observational studies
- 1 x Animal RCT
- 1 large human RCT

Observational Studies

Lead Author	Year	Journal	Patients	Pros/Retro
Alsous	2000	Chest	36	Retro
Vincent	2006	Crit Care Med	1177	Pros
Rosenberg	2009	J of Int Care Med	844	Pros + post hoc
Boyd	2011	Crit Care Med	778	Retro
Micek	2013	Crit Care	163	Retro

Key points

- *Positive fluid balance (early & late) was a strong independent predictor of mortality*
- Vincent 2006, SOAP study
  - OR 1.1 increased mortality per litre excess fluid
- Rosenberg 2009 ARDS Net
  - Cumulative negative fluid balance by day 4 OR 0.5 for reduced mortality

Limitations of Observational Studies

- Positive fluid balance ≠ fluid administration
- Potential confounders eg shock severity
- However in most studies, positive fluid balance was an independent risk factor after multivariate logistic regression so key known confounders accounted for
- Unknown or unmeasured confounders may still be relevant


The Three Little Pigs
source: http://learninghousejaipur.files.wordpress.com

RCT in Pigs...

- Brandt, Crit Care 2009
- 48 pigs randomised in 3 groups:
  - 1. faecal peritonitis
  - 2. endotoxin infusion
  - 3. control
- Then randomised to 2 treatments:
  - moderate volume (10ml/kg/hr)
  - high volume (20ml/kg/hr)

RCT in Pigs …

- Results:
  - **Improved haemodynamics** in high vol group
    - Improved CI, higher MAP, lower lactate

  BUT:

  - **Increased mortality** in high vol group
    - Peritonitis: 87% v's 50%
    - Endotoxemia: 75% v 13%
    - Controls: 13% v 0%


http://
www.drawergeeks.com

RCT in Humans

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med., Charles Engoru, M.B., Ch.B., M.Med., Peter Olupot-Olupot, M.B., Ch.B., Samuel O. Akech, M.B., Ch.B., Richard Nyeko, M.B., Ch.B., M.Med., George Mtove, M.D., Hugh Reyburn, M.B., B.S., Trudie Lang, Ph.D., Bernadette Brent, M.B., B.S., Jennifer A. Evans, M.B., B.S., James K. Tibenderana, M.B., Ch.B., Ph.D., Jane Crawley, M.B., B.S., M.D., Elizabeth C. Russell, M.Sc., Michael Levin, F.Med.Sci., Ph.D., Abdel G. Babiker, Ph.D., and Diana M. Gibb, M.B., Ch.B., M.D., for the FEAST Trial Group*

RCT in Humans

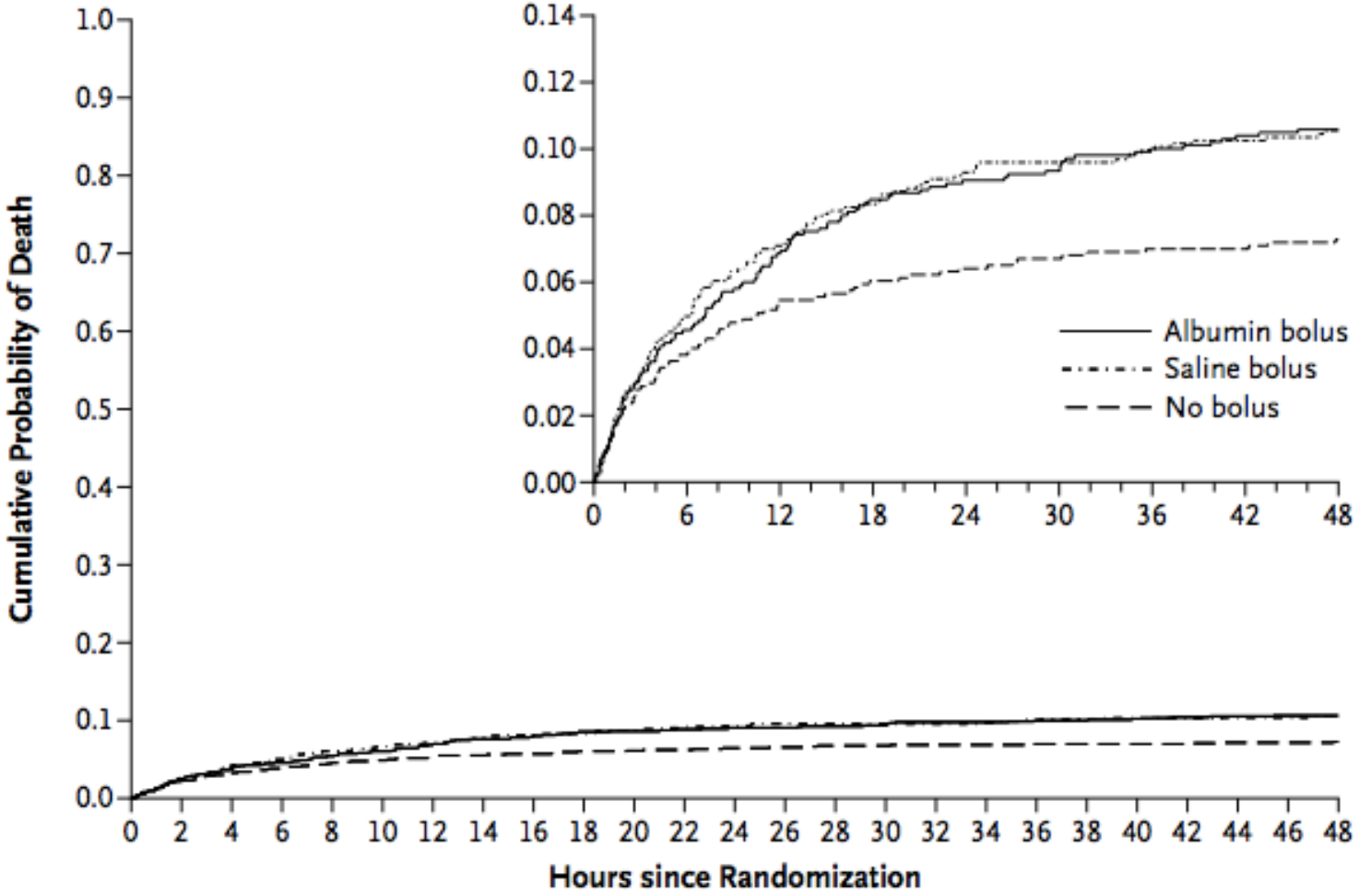
- **FEAST Trial, Maitland, NEJM 2011**
- Large, well conducted RCT in Africa: **3141 patients**
- Investigated the effect of fluids in children with septic shock
- Patients randomised into 3 groups
  - Intervention 1: 20ml/kg normal saline bolus
  - Intervention 2: 20ml/kg albumin bolus
  - Control: no bolus
  - Note – all groups received maintenance fluids
- Excluded hypovolaemic conditions i.e gastroenteritis

Results

- *Increased mortality in the fluid bolus group*
  - **Increased RR mortality = 45%**

	Albumin	Saline	Control
48hr	10.6%	10.5%	7.3%
4 week	12.2%	12.0%	8.7&

A **Mortality at 48 Hours**



	Hr 1			Hr 2			Hr 3			Hr 4			Hr 5–8			Hr 9–24			Hr 24–48		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	1037	1033	1030	1024	1018	1021	1016	1010	1015	1010	1001	1011	992	980	996	954	945	975
Died	13	12	14	13	15	9	8	7	6	6	9	4	17	20	14	38	34	20	16	13	9
%	1.2	1.1	1.3	1.3	1.5	0.9	0.8	0.7	0.6	0.6	0.9	0.4	1.7	2.0	1.4	3.8	3.5	2.0	1.7	1.4	0.9

Sub-groups

- Results were consistent across *every single sub-group* including
  - Severity of shock
  - Presence of malaria or anaemia
  - Coma
  - Type of sepsis
  - Acidosis
  - Lactate level
  - = *LIKELY REAL FINDING*

Criticisms→ Refuted

- High malaria prevalence (57%)
  - → Same findings with and without malaria
- High anaemia prevalence
  - → Same findings with and without anaemia
- Clinical measures of shock may have over-estimated the children with septic shock
  - → Most severe shock cases had the greatest harm from fluid boluses: 10% v 3% mortality

Criticisms → Refuted …

- No 1st world ICU care
  - → ICU care may have masked fluid harms but is no reason not to prevent the harm in the first place
- Could be an effect of *saline* in N/S and albumin
  - → possible though see re-analysis
- In kids not adults
  - → perhaps relevant if death by fluid overload
    - see re-analysis

Re-analysis of FEAST

- Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial
  - Maitland et al, BMC Medicine 2013
- Causes of death after fluid bolus resuscitation: new insights from FEAST
  - Myburgh & Finfer, BMC Medicine 2013

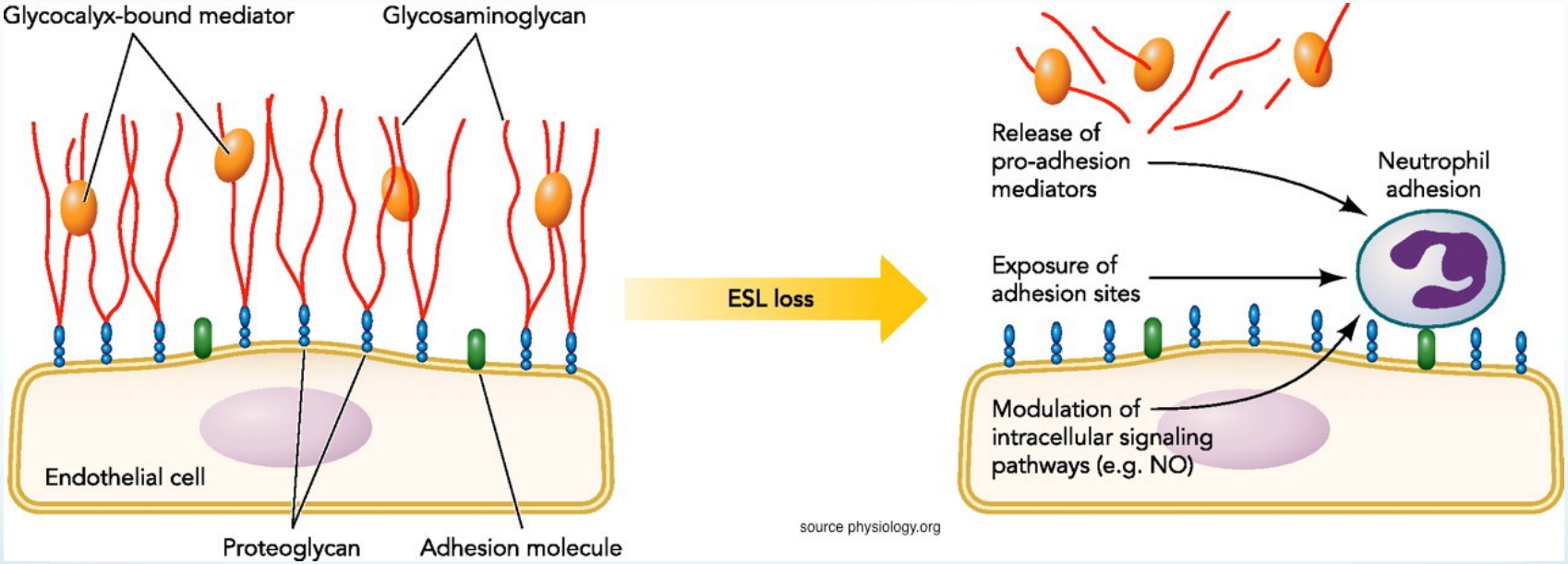
Criticisms Refuted: Reanalysis

- Cause of death was *not* fluid overload!
- Cause of death that increased in the bolus group = cardiovascular collapse!
- This was despite the bolus group having an initial improvement in haemodynamics
  - Doctors were shocked by the results
  - *Our anecdotal experience is no longer reassuring*

Proposed mechanisms of harm from fluids

- Cardiovascular collapse
  - Undermining sympathetic compensation
  - Reperfusion injury
  - Injury to the Endothelial Glycocalyx (EG)
    - Shear forces on EG
    - Atrial stretch releasing ANP and BNP which damage EG harm
- Net result is increasing vasodilation and capillary permeability → cardiovascular collapse
  - … chasing our tail with additional fluids

Endothelial Glycocalyx



Balance of fluid resus evidence?

- **FOR:**
  - 1 observational study (10 pts per arm)
  - + Rivers EGDT (260 pts)

Vs

- **AGAINST:**
  - PROMISE & ARISE debunking EGDT (3000 pts)
  - Several observational studies (3000 pts)
  - + 1 animal RCT (48 pigs)
  - + 1 human RCT (3000 pts)

Resuscitation End Points in Sepsis

- 1. Adequate MAP
  - ? 65mmHg
- 2. Adequate tissue perfusion
  - Relatively normal CR (<4 sec)
  - Peripheral warmth
  - Absence of skin mottling
  - Lactate <2
  - Urine output > 0.5ml/kg/hr
- **Assuming** these targets are worthy endpoints:
  - *the journey may be as important as the destination*

Choice of journey

- *Aggressive* fluid resus followed by *late* use of noradrenaline

OR

- *Conservative* fluid resuscitation combined with *early* use of noradrenaline

Treatment of vasodilatory shock

- **Anaphylaxis:**
  - *Adrenaline, Adrenaline, Adrenaline*

- **Sepsis:**
  - *Fluids, Fluids, Fluids*
  - then… not in pulmonary oedema?
    - give some more fluids
      - … *then* norad

Why don't we currently use noradrenaline early?

- 1. Requires a central line
  - → Wrong
  - Ricard et al, *Critical Care Medicine* 2013
    - Used up to 33mcg/min of vasopressors peripherally
- 2. Commits patients to an ICU/HDU
  - → Excellent!
- 3. Could it be harmful?

Noradrenaline in septic shock

- Bellomo, Critical Care 2001
- Hamzoui Critical Care 2007
- Hamzoui Critical Care 2010
- Perishini Critical Care Medicine, 2012

Hamzoui, Critical Care 2010

- Observational study re *early* admin of norad
  - 105 patients admitted to ICU for less than 6 hours
  - ½ had norad started already → increased.
  - Other ½ had norad started
  - Median volume fluid administered prior was *only* 1L (0.5-1.5L)

Hamzoui, Critical Care 2010…

- **Results***:*
  - *Early* administration of norad increases preload, contractility and CO
  - Finding was true regardless of LVEF *unless:*
    - Patients had LVEF < 45% AND MAP > 75mmHg

- *Who said you need to fill the tank before you tense it?*

Noradrenaline Summary

- In *hypotensive vasodilated septic shock patients* noradrenaline increases:
  - Preload
  - CO
  - Renal blood flow and function
- When MAP increases beyond 75mmHg this may not be the case in patients with poor LEVF

From: Early Management of Severe SepsisManagement of Sepsis: Concepts and Controversies

Chest. 2014;145(6):1407-1418. doi:10.1378/chest.13-2104

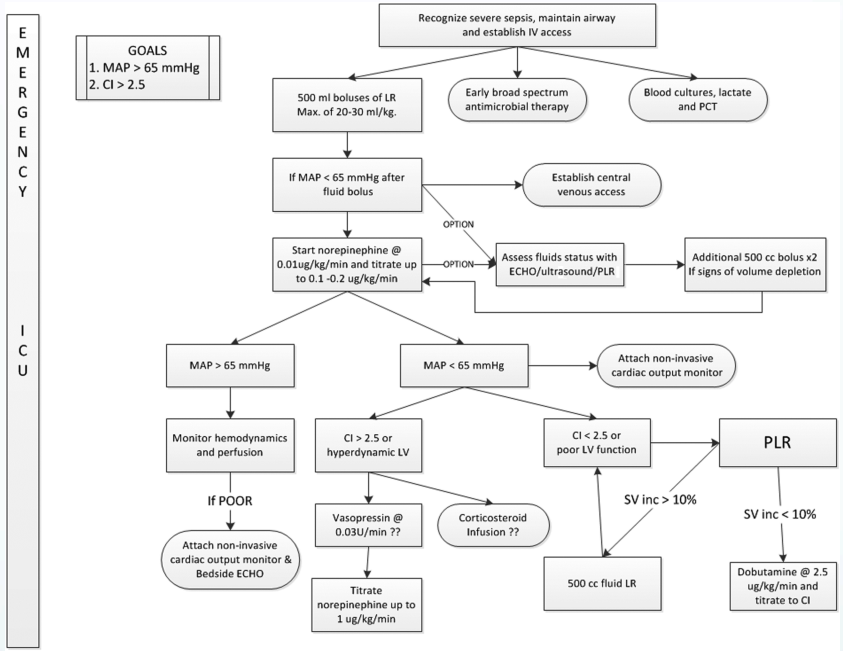
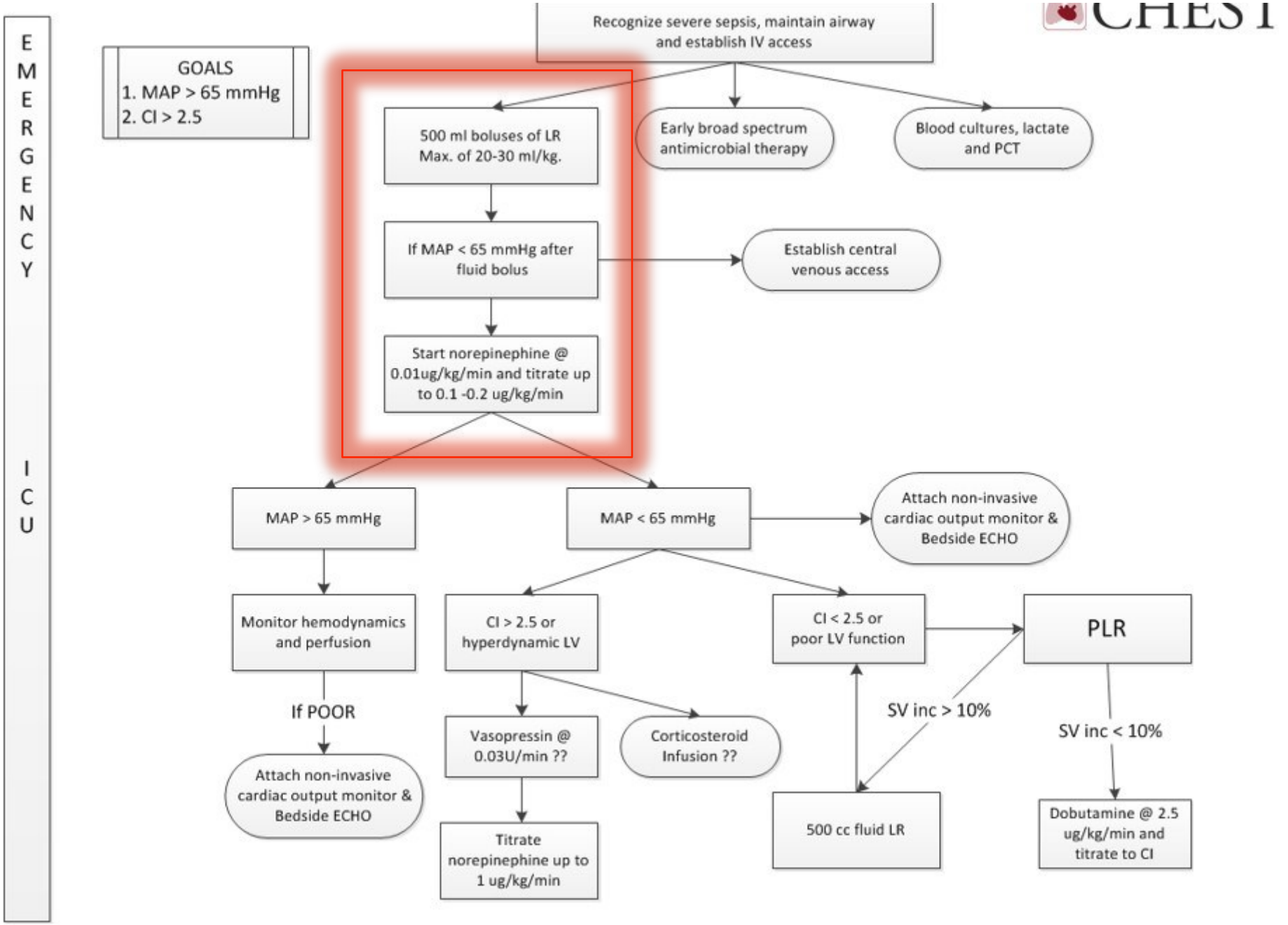


Figure Legend:

Suggested initial approach to the management of patients with severe sepsis and septic shock. CI = cardiac index; ECHO = echocardiography; inc = increase; LR = Lactated Ringers solution; LV = left ventricle; MAP = mean arterial pressure; Max = maximal; PCT = procalcitonin; PLR = passive leg raising; SV = stroke volume.



Marik PE. Chest 2014 (in press)

Fluids in ARISE

- ARISE gave 1960ml v 1710ml of fluid in EGDT v Controls in 1st 6 hours
- Mortality rate = 19%

Take Home Messages

- 1. Target MAP *and* tissue perfusion goals but the *journey maybe as important as the destination*
  - Our focus on short term haemodynamics *may* be misguided and misleading
- 2. Rapid fluid *boluses* and high cumulative *volumes* may increase mortality in septic shock
  - Consider using smaller *volumes/rates* than usual practice
- 3. Consider *early* use of low dose noradrenaline (eg via *good quality* peripheral IVC)

Acknowledgements

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- Dr Paul Marik

Questions

- @drsenthi

- Emergucate.com
  - *Talk is posted here with references*