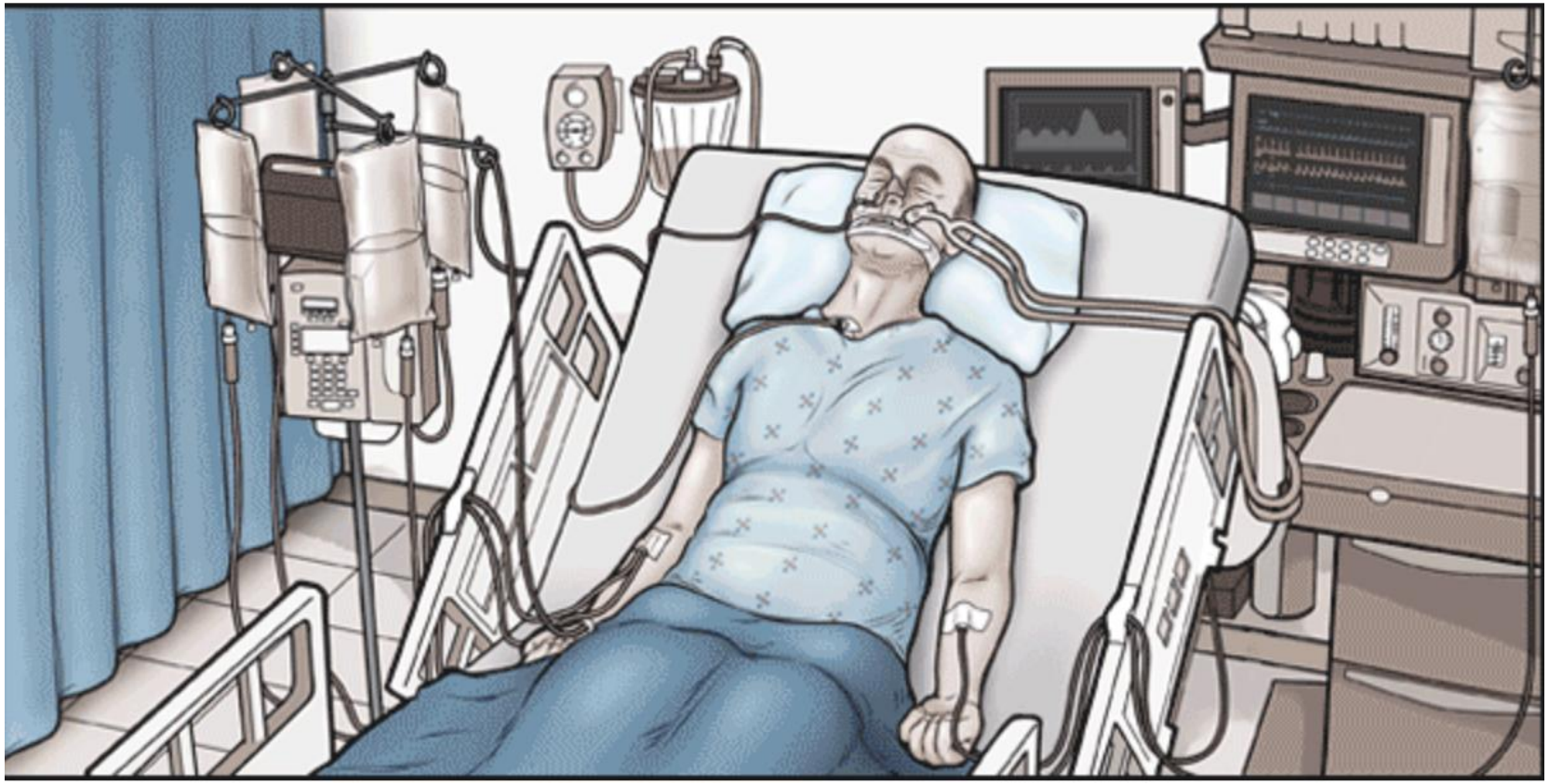
Fluid resuscitation debates: Crystalloid vs Colloid, early Vasopressors

黃俊德
台中榮民總醫院
數位醫學部 人工智慧科
重症醫學部 重症加護內科
內科部 腎臟科



77 歲 男性

慢性病史：
高血壓，高血脂，酗酒

入院原因：
perforated sigmoid colon with fecal peritonitis

入ICU時狀況：
接受Hartmann's procedure,
4000ml crystalloid in OR

Vital sign upon ICU arrival
BP: 88/52 mmHg
HR:120 bpm
CVP:6 mmHg
T: 35.6℃

PE:
Peripherally cold
Prolonged capillary refill

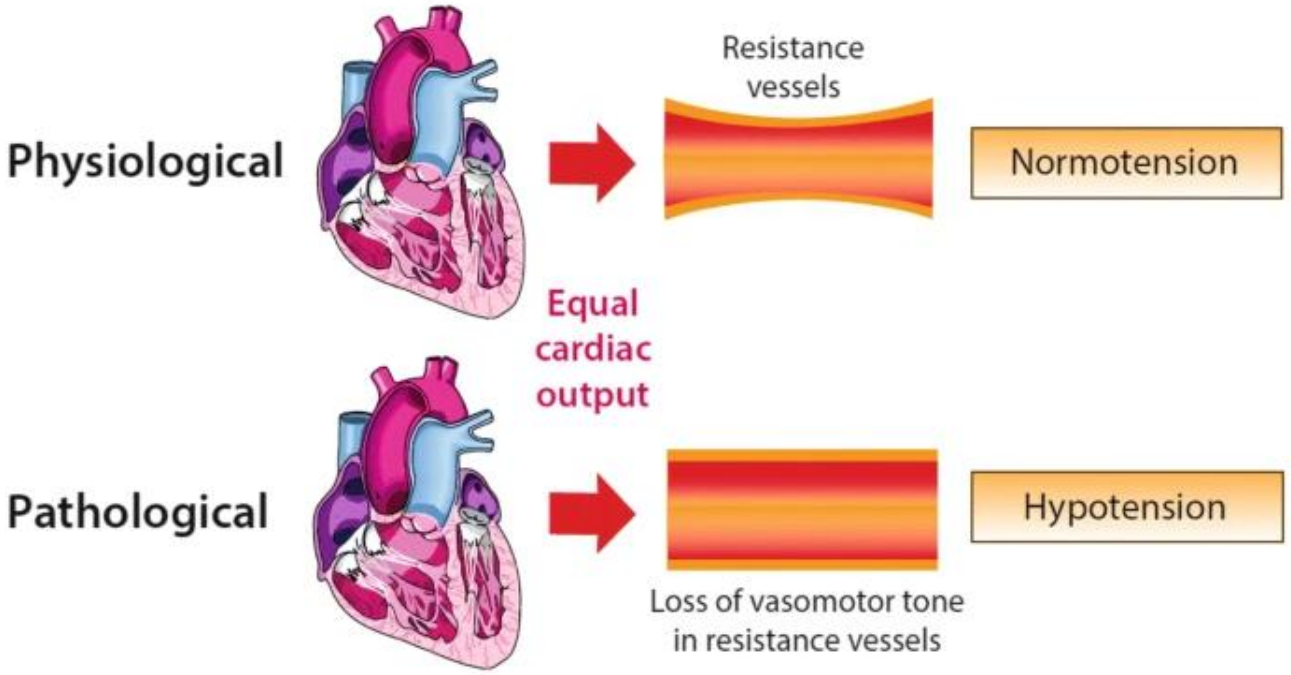
Lab data:
ABG: pH:7.32/PaCO2:28/PaO2:85
Lactate:27.5 mg/dL
Na:142/K:4.4/Cl:109
BUN:22
Cr:2.3
Alb:2.3
Urine: 28ml/2 hours

Tentative Diagosis

Perforated sigmoid colon with fecal peritonitis s/p Hartmann's procedure complicated in septic shock and possible acute kidney injury

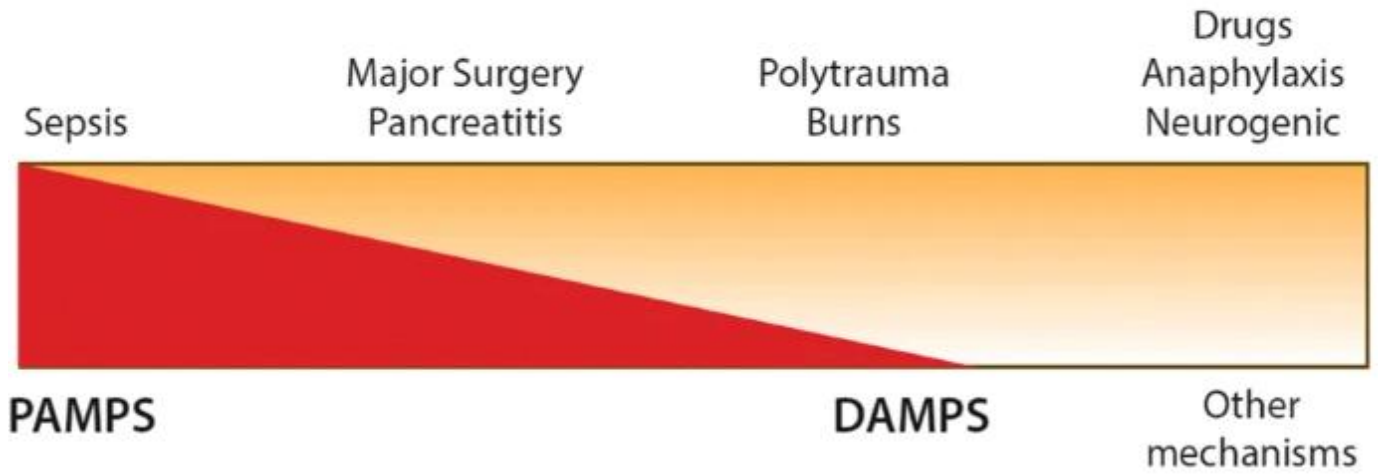

1000 ml
LACTATED RINGER'S
injection, USP
1000 ml
ALBUMIN
injection, USP
1000 ml
6% HETASTARCH
injection, USP
1000 ml
SALINE
injection, USP
High Dose Vasopressor
• Combined Noropinephrine Vasopressin or Epinephrin
• Late Vasopressor Risks
• Volume overload
• Increased mortality

Fig. 1

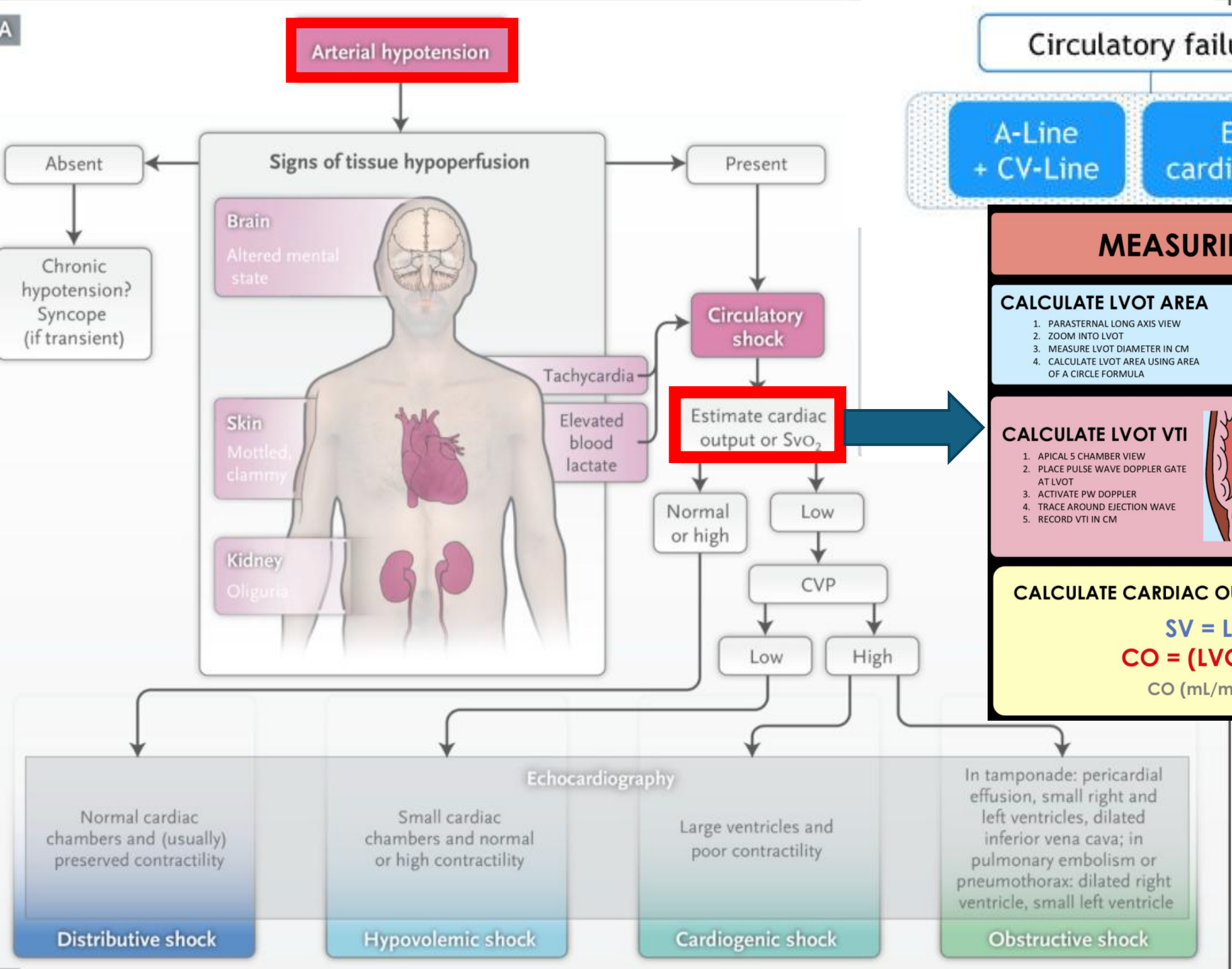


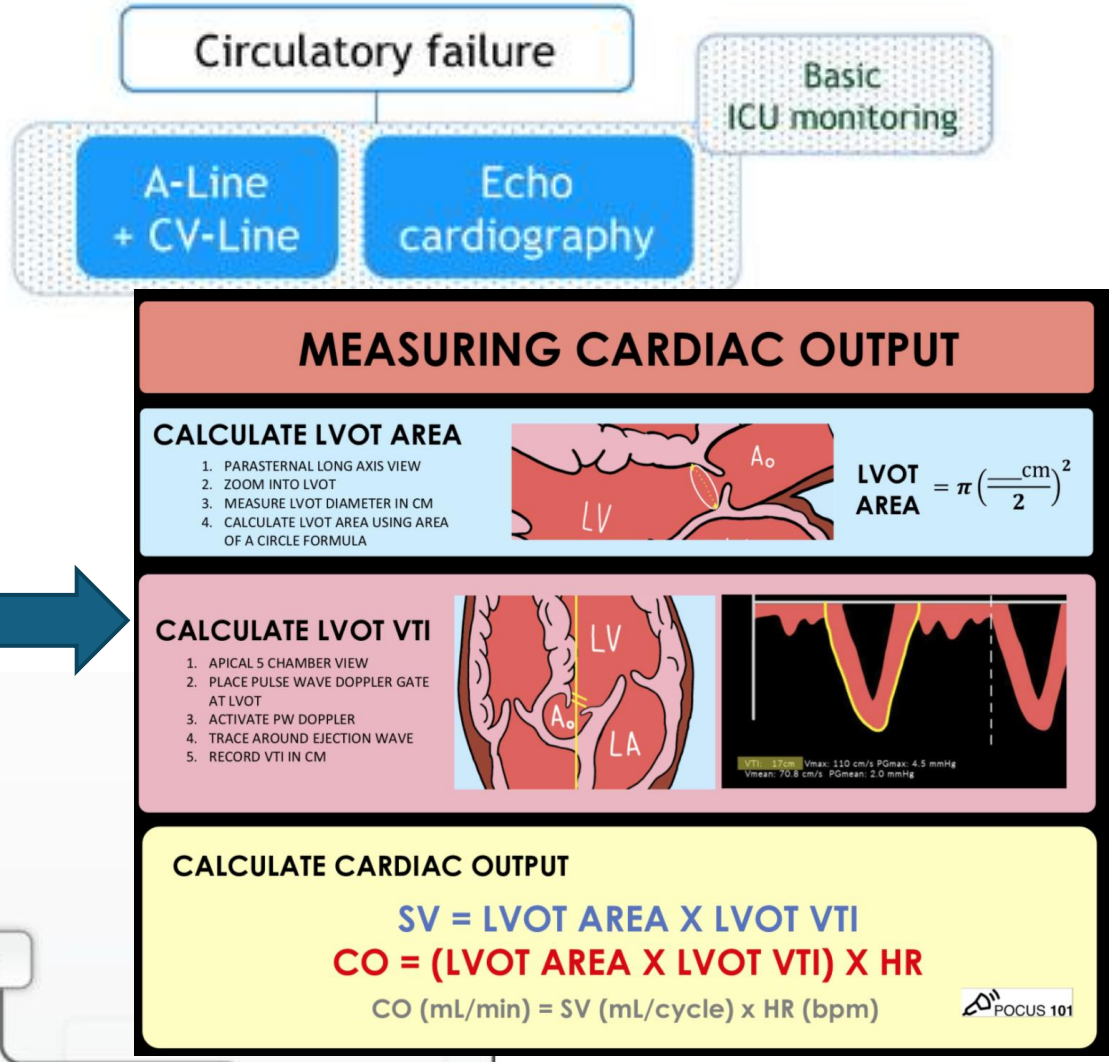
BP =	CO		x	SVR
	Cardiac Output			Systemic Vascular Resistance
	(SV x HR)			
	Stroke Volume	Heart Rate		
	Preload Contractility Afterload			

Fig. 2

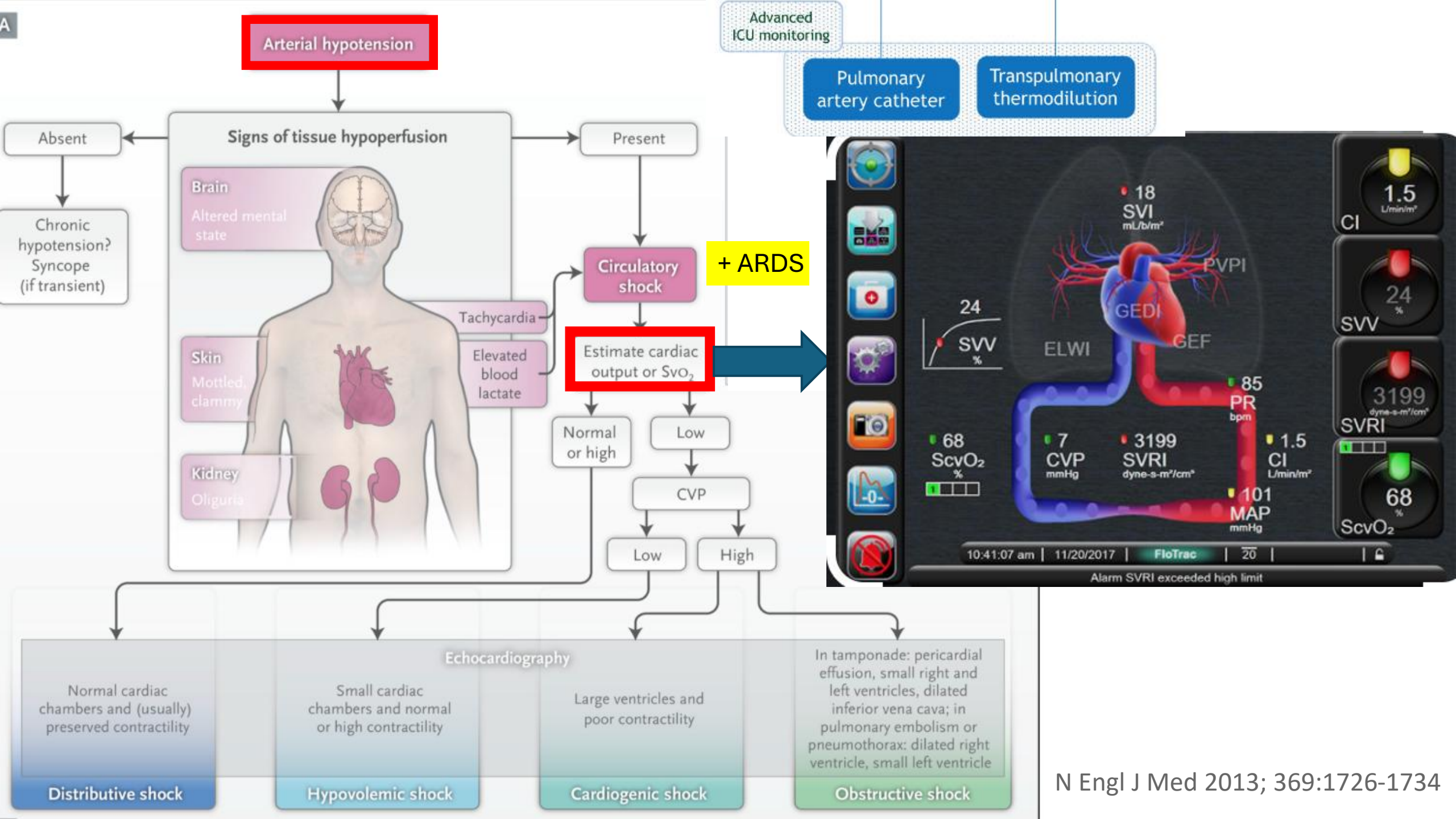


Lambden, S. et al. *Crit Care* **22,** 174 (2018)

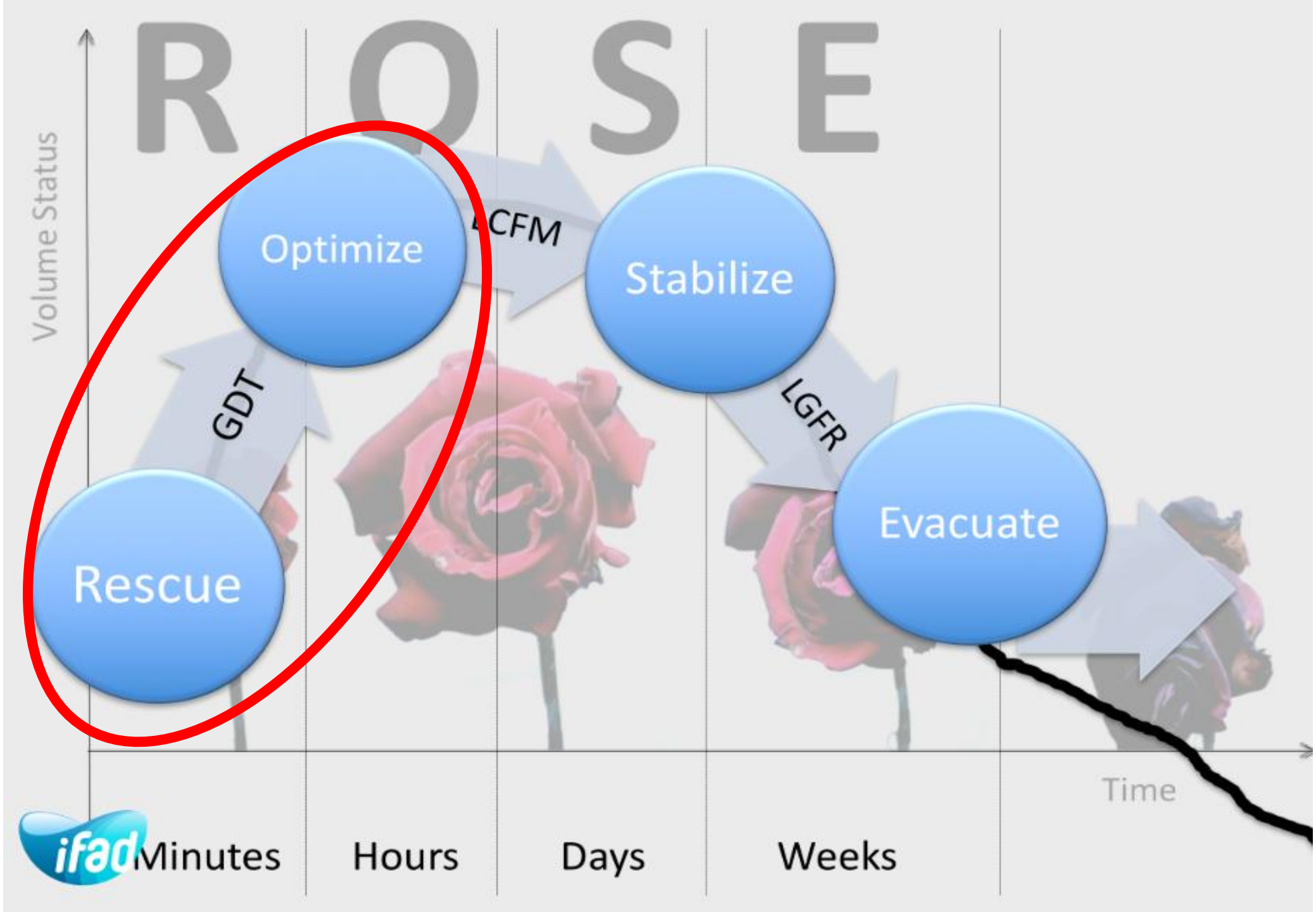




N Engl J Med 2013; 369:1726-1734



N Engl J Med 2013; 369:1726-1734

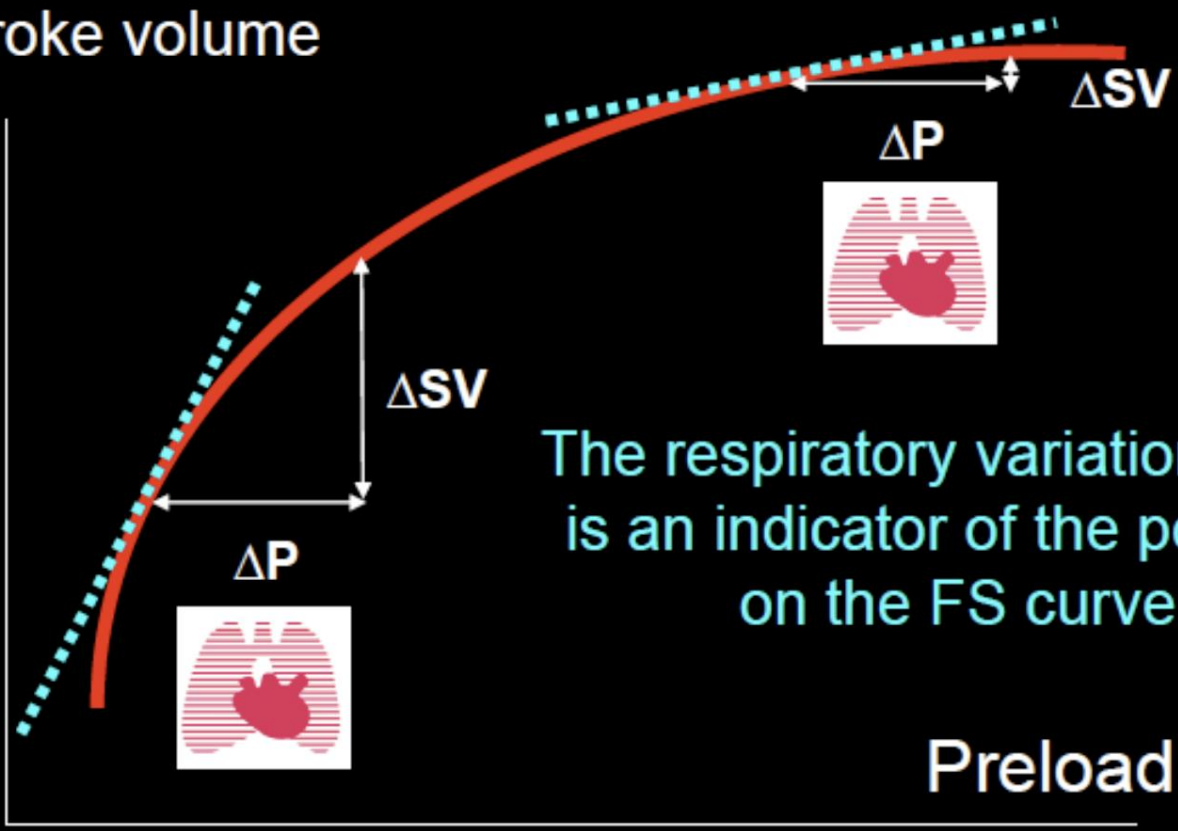

R O S E
Volume Status
Optimize
CFM
Stabilize
GDT
LGFR
Rescue
Evacuate
Time
Minutes
Hours
Days
Weeks

Fluid responsiveness

- Ability of a test or an observation to predict whether an individual patient is going to benefit from administration of a fluid bolus

- Outcome measure usually significant increase in stroke volume (cardiac output)

Meaning



The respiratory variation in SV is an indicator of the position on the FS curve

臺中榮民總醫院
Taichung Veterans General Hospital

Dynamic hemodynamic variable

- Stroke Volume Variation (SVV)
- Pulse Pressure Variation (PPV)
- Passive Raising Leg Test →Δ CO or Δ SVI
- End Expiratory Occlusion Test →Δ CO or Δ SVI
- Fluid challenge →Δ CO or Δ SVI
- Inferior Vena Cava Variation


1000 mL
LACTATED RINGER'S
injection, USP
1000 mL
ALBUMIN
injection, USP
1000 mL
6% HETASTARCH
injection, USP
1000 mL
SALINE
injection, USP

輸液治療的四大功能

1. Resuscitation（復甦）：迅速恢復血容量與灌流
2. Maintenance（維持）：每日水分與電解質補充
3. Nutrition（營養）：PPN, TPN 等高張液體
4. Metabolic modulation（代謝調控）：例如白蛋白、重碳酸鈉調整酸鹼

Crystalloid

- **Balanced crystalloid**：如Lactated Ringer、Plasmalyte，
- **Unbalanced crystalloid**：如Normal Saline，

Colloid

- **Albumin**：天然膠體液，高滲透壓，常用於肝硬化、SBP、腎功能障礙伴隨低蛋白血症病人。
- **Synthetic colloid（合成膠體）**：如HES（羥乙基澱粉）或Gelatin

輸液種類簡介

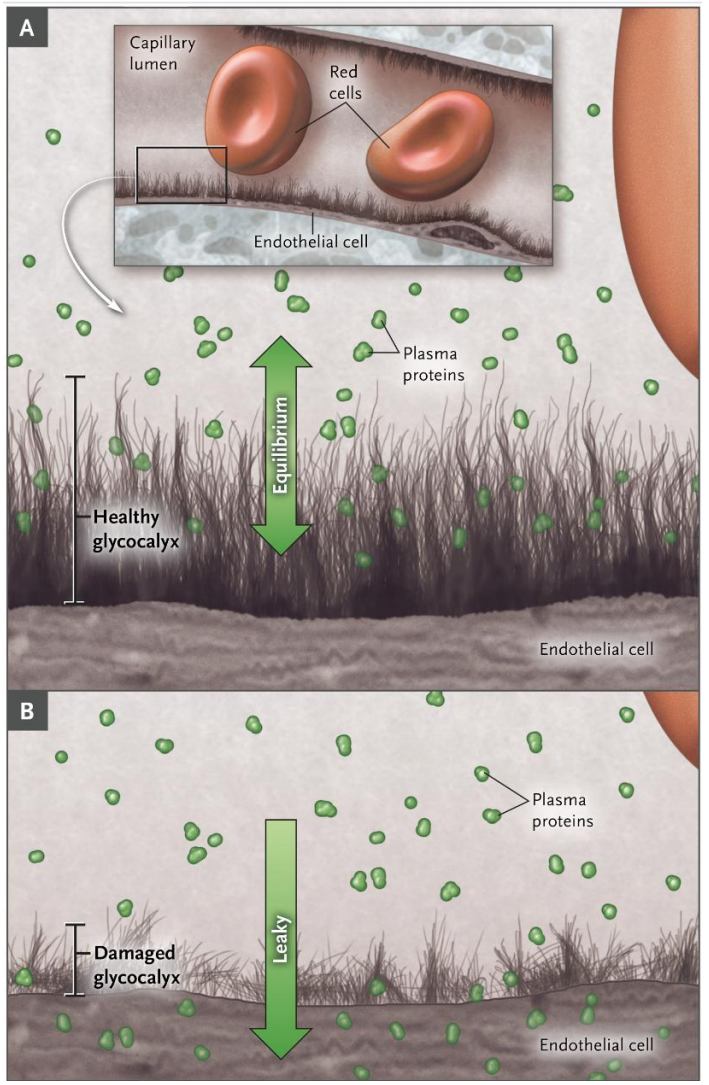
液體類型	成分特色	常見用途
Normal Saline (NS)	高鈉高氯，pH偏低	Volume resuscitation, hyponatremia
Lactated Ringer	含乳酸緩衝劑，接近體液組成	Balanced resuscitation, burn, trauma
Plasma-Lyte (台灣沒有)	Balanced, 含醋酸與葡萄糖酸	代謝性酸中毒，避免氯酸中毒
Albumin	高滲透膠體	Cirrhosis, SBP, HRS, hypoalbuminemia

中榮常見點滴成分比較表

	0.9% Normal Saline	Lactated Ringer	Plasma-Lyte	D5W	D10W	0.9% Saline+5% GW	0.45% Saline+5% GW	3% Saline	Taita No.2	Taita No.5
Na (mmol/L)	154	130	140	0	0	154	77	513	40	36
K (mmol/L)	0	4	5	0	0	0	0	0	12	18
Cl (mmol/L)	154	109	98	0	0	154	77	513	26	17
Ca (mmol/L)	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0	3.0
Mg (mmol/L)	0.0	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0	2.0
Glucose (g/L)	0	0	0	25	50	25	25	0	33	100
Bicarbonate (mmol/L)	0	28	0	0	0	0	0	0	0	0
pH	5.5	6.5	7.4	4.5	4.5	4.5	4.5	5.0	4.0-7.5	5-6
Osmolarity (mOsm/L)	308	273	294	278	555	586	432	1026	287	669
Tonicity	Isotonic	Isotonic	Isotonic	Hypotonic	Hypotonic	Hyper->Isotonic	Hyper->Hypotonic	Hypertonic	Isotonic	Hypertonic

Sepsis Pathophysiology

1. Loss glycocalyx
2. Loss vascular vessel tone

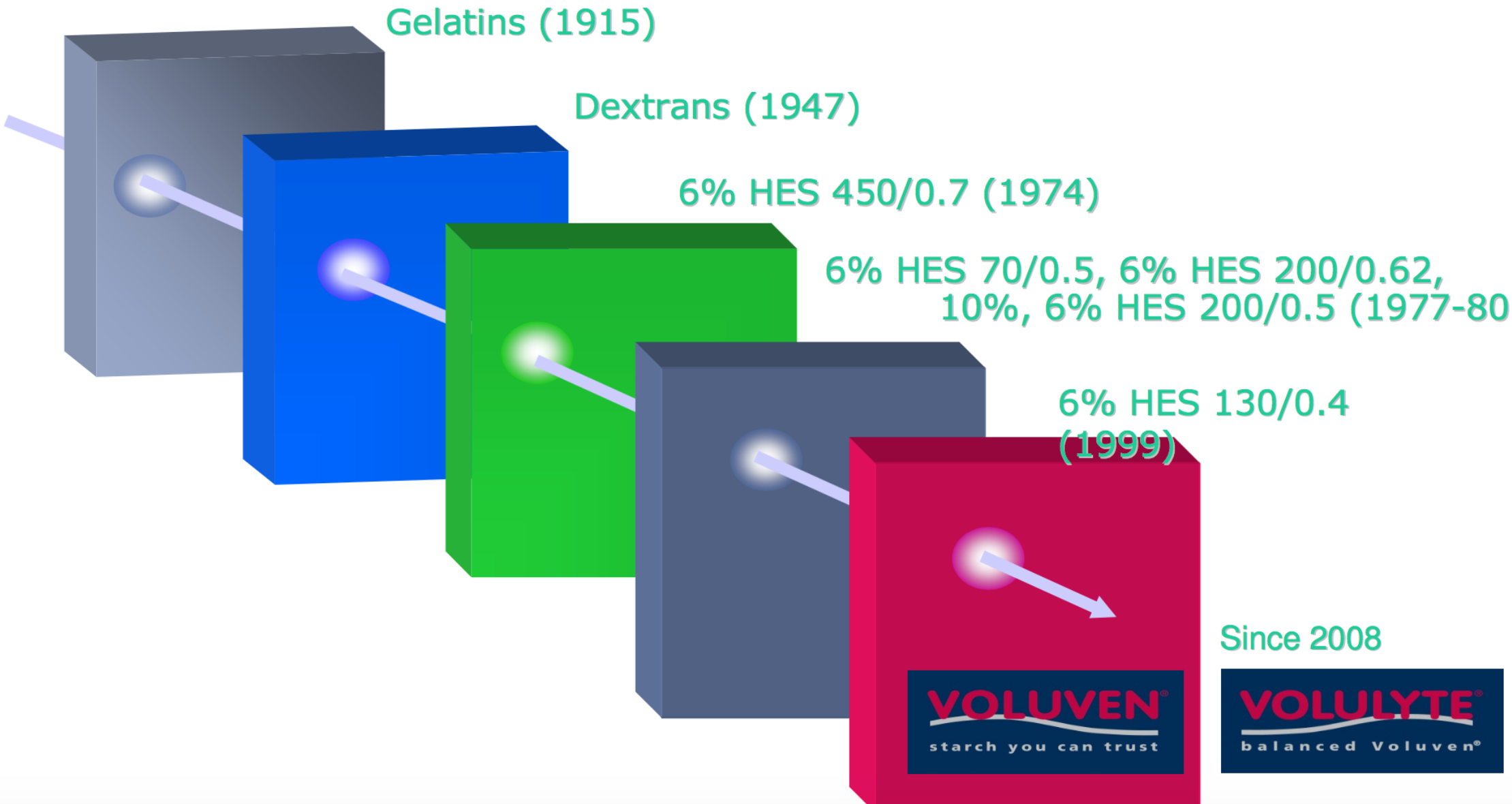


Hypothesis

Could colloid maintain intravascular volume and alleviate fluid overload during sepsis resuscitation?

Synthetic Colloid History

FRESENIUS KABI



The Retraction Watch Leaderboard

with 21 comments

Who has the most retractions? Here's our unofficial list (see notes on methodology), which we'll update as more information comes to light:

1. Yoshitaka Fujii (total retractions: 183) Sources: Final report of investigating committee, our reporting
2. Joachim Boldt (96) Sources: Editors in chief statement, additional coverage
3. Diederik Stapel (58) Source: Our cataloging
4. Adrian Maxim (48) Source: IEEE database
5. Peter Chen (Chen-Yuan Chen) (43) Source: SAGE, our cataloging
6. Hua Zhong (41) Source: Journal
7. Shigeaki Kato (39) Source: Our cataloging
8. James Hunton (37) Source: Our cataloging
9. Hendrik Schön (36) Sources: PubMed and Thomson Scientific
10. Hyung-In Moon (35) Source: Our cataloging
11. Naoki Mori (32) Source: PubMed, our cataloging
12. Tao Liu: (29) Source: Journal
13. Cheng-Wu Chen (28) Source: our cataloging
14. Gideon Goldstein (26)

Can J Anesth/J Can Anesth (2011) 58:777–781
DOI 10.1007/s12630-011-9558-7

EDITORIALS

Update to readers and authors on ethical and scientific misconduct: retraction of the "Boldt articles"

Donald R. Miller, MD

There are over 50 published randomized controlled trials evaluating HES 130/0.4.

Hydroxyethyl Starch（HES）安全性爭議與 Boldt 案事件始末

背景Joachim Boldt：德國麻醉學者，曾被視為術中液體管理領域權威。發表約 **350 篇論文**，多數研究顯示 **HES（Hydroxyethyl starch）** 在手術與重症中「安全且有效」。其研究結果深深影響臨床指引與麻醉學教材。

2009 年：研究不端揭發德國醫學界發現其多篇研究 **未經倫理審查與病人同意書**。後續調查揭露 **資料造假與偽造數據**。超過 **90 篇論文被撤稿（retracted）**，學界震撼。

2010–2012 年：臨床證據重估移除 Boldt 研究後的 **系統性回顧與 meta-analysis**（加拿大 Critical Care Trials Group）：發現重症患者使用 HES 有 **腎損傷與死亡風險上升趨勢**。**Boldt 研究的排除反而提高 HES 的安全疑慮。**

6S Trial 2012 NEJM

北歐（丹麥、芬蘭、挪威、冰島，約 30 間 ICU）

•商品名 **Tetraspan 6%**（B. Braun）

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,
Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,
Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D.,
Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D.,
Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D.,
Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D.,
Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D.,
Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D.,
Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D.,
for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

CHEST Trial 2012 NEJM

澳洲與紐西蘭（澳大利亞／New Zealand ICU 多中心）

•商品名 **Voluven**，**Fresenius Kabi**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D.,
Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D.,
Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D.,
Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D.,
and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators
and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

	6S Trial	CHEST Trial
研究名稱	*Hydroxyethyl Starch 130/0.42 vs Ringer's Acetate in Severe Sepsis*	*Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care*
主要族群	嚴重敗血症（Severe sepsis）	所有 ICU 病人（含敗血症、外傷、術後等）
比較組別	HES 130/0.42 vs Ringer's acetate	HES 130/0.4 vs 0.9% NaCl
樣本數	N = 798 (400 vs 398)	N = 7000 (3500 vs 3500)
HES 劑量上限	33 mL/kg/day	50 mL/kg/day
主要結果	HES 組死亡率↑、洗腎風險↑	HES 組洗腎風險↑ 死亡率無顯著差異
結論摘要	HES 在敗血症病人中增加死亡與腎傷害風險	HES 無生存獲益，並增加腎損傷風險，不建議常規使用

Cristal Trial 2013 JAMA

2003-2012
族群：重症病患
有 低血容量性休克 **(hypovolemic shock)**
包含原因：
•敗血症（sepsis）
•外傷（trauma）
•消化道出血、手術後失血等

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

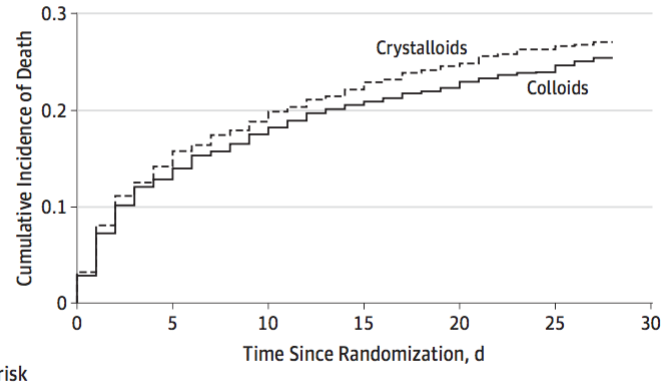
Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

Colloid(Albumin, HES, Gelatin, Dextran) N=1414

Crystalloid (0.9%NaCl, Ringer) N=1443

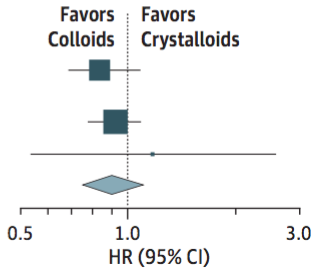
Figure 2. Cumulative Incidence of Death Within First 28 Days After Randomization



No. at risk						
Colloids	1414	1233	1167	1124	1099	1076
Crystalloids	1443	1239	1172	1124	1089	1064

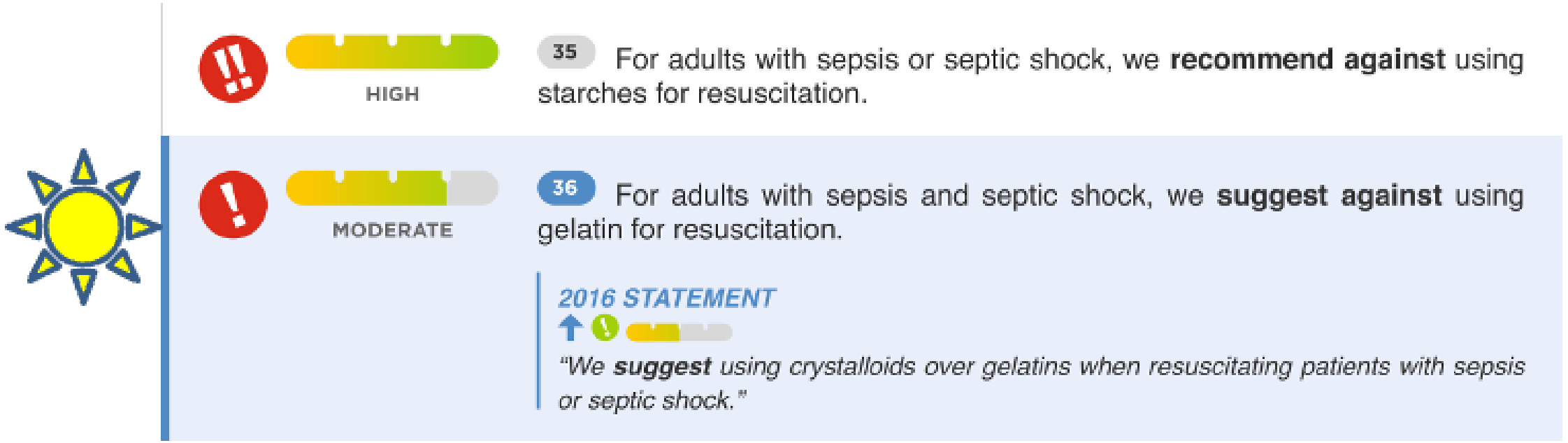
Figure 3. Assessment of Treatment × Diagnosis Interaction and Death Within First 28 Days

Reason for ICU Admission	Colloids Group (n = 1414) No. of Patients	Colloids Group (n = 1414) No. of Deaths	Crystalloids Group (n = 1443) No. of Patients	Crystalloids Group (n = 1443) No. of Deaths	HR (95% CI)
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)
Sepsis	774	215	779	226	0.95 (0.78-1.10)
Trauma	85	13	92	12	1.19 (0.54-2.60)
All patients	1414	359	1443	390	0.93 (0.80-1.10)



28-day mortality no difference (25.4% vs 27.0%, p:0.26)

2021 Sepsis Guideline



Synthetic colloid（合成膠體）：如HES（羥乙基澱粉）或Gelatin，過去用於volume resuscitation，但現今研究顯示可能增加腎損傷風險與凝血功能障礙，使用上需特別謹慎。

Boldts affair

- Joachim Boldt 於 2011 年被德國檢察官起訴，2013 年被法院判決有罪（偽造與詐欺），處以緩刑與罰金。

- 這起事件被稱為「Boldt affair」，導致全球撤稿潮並重塑臨床研究倫理與 HES 安全評估。

Fresenius Kabi 敗訴：
歐盟法院維持 HES 暫停上市決議

European Commission（EC）於 2022 年5 月作出的《實施決定 C(2022) 3591 final》，要求歐盟會員國暫停含有 Hydroxyethyl starch（HES）輸液製品的上市許可（MAs）後，Fresenius Kabi Austria GmbH 等藥廠向 General Court of the European Union（案件號 T-416/22）提出撤銷該決定的請求。

法院於 2024 年5 月15 日做出判決，**駁回** Fresenius Kabi 等申請人的撤銷請求，認為該決定合法且符合相關法令。

Albumin??

The NEW ENGLAND JOURNAL of MEDICINE

2004 SAFE study

ORIGINAL ARTICLE

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

The SAFE Study Investigators*

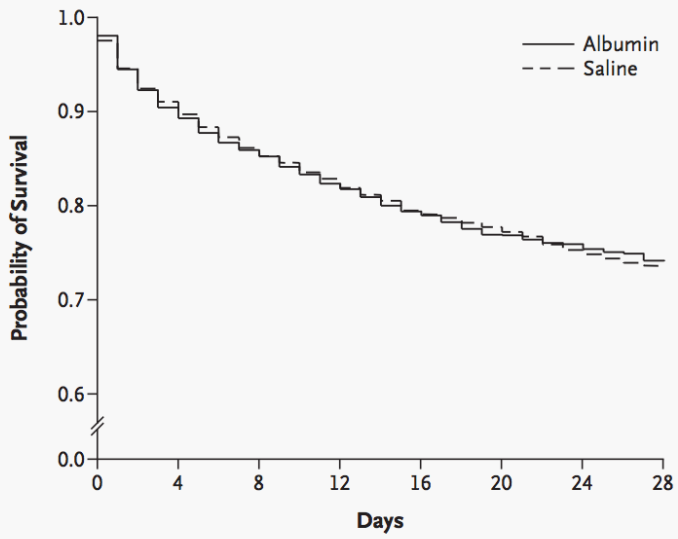


Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.

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)

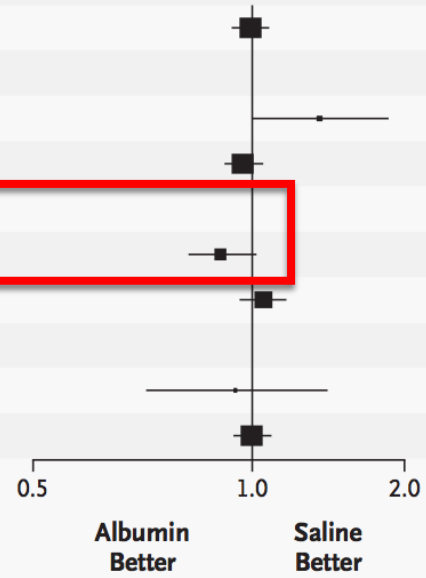


Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.
The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.

2014 ALBIOS study

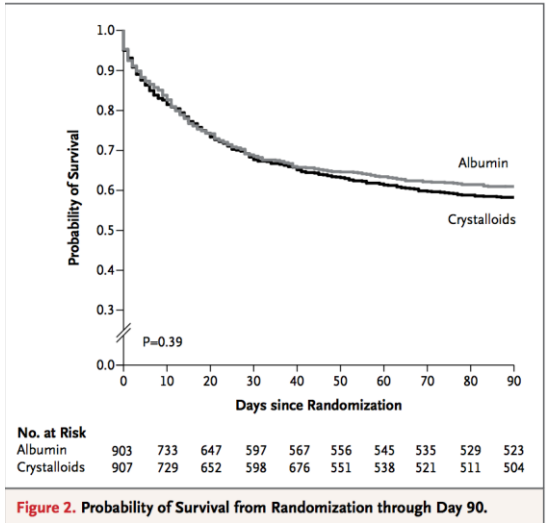


Figure 2. Probability of Survival from Randomization through Day 90.

28 天死亡率（31.8% vs 32.0%）無顯著差異

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

組別	給液策略	Albumin 目標	液體種類
Albumin + Crystalloid 組	0.9% NaCl 或 Lactated Ringer's + 20% Albumin	維持 **血清白蛋白濃度 ≥ 30 g/L**	20% Albumin (平均每日 300 mL)
Crystalloid-only 組	僅使用 Crystalloid（無 Albumin）	無	0.9% NaCl / LR

次要結局	結果
90 天死亡率	41.1% vs 43.6%（p = 0.29）無顯著差異
休克亞組分析	在 **septic shock** 病人中 **Albumin 組 90** 天死亡率較低 (43.6% → 49.9%, *p = 0.03*)
MAP	Albumin 組平均 MAP 較高、所需升壓劑劑量較少
液體總量	Albumin 組使用液體體積較低

2021 Sepsis Guideline

Albumin

34 For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids.

- Albumin 可視為 **第二線液體**，當高流量晶體液已達上限、或需減少液體負荷時考慮。
- 不建議常規用於所有敗血症病人。

Fluid choice and AKI

➢Balanced crystalloid

- **SPLIT trial 2015 JAMA**
- **SALT-ED trial 2018 NEJM**
- **SMART trial 2018 NEJM**
- **BaSic trial 2021 JAMA**
- **PLUS trial 2022 NEJM**

Tubulo-glomerular feedback

Hyperchloremia

↓

Afferent arterial vasoconstriction

↓

↓↓↓GFR

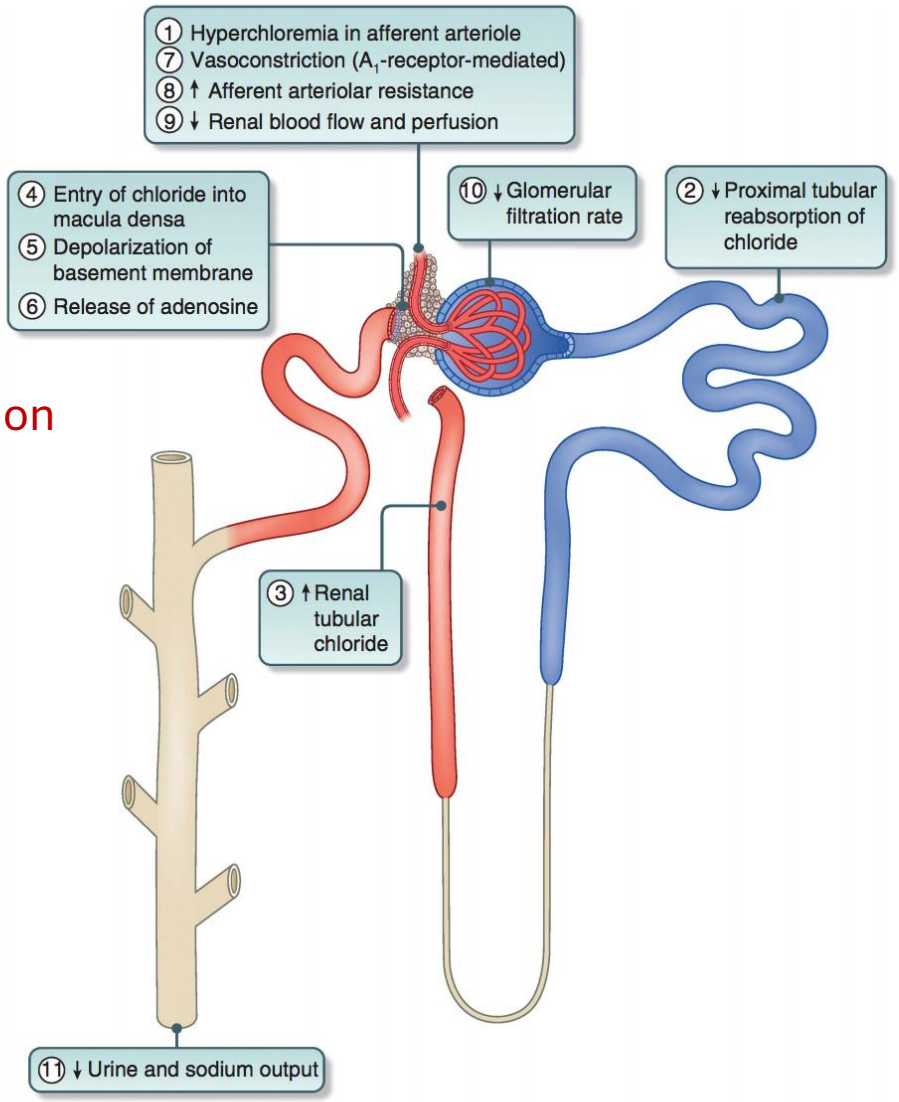


Figure 2 | Schematic diagram of the sequential effects of hyperchloremia on the kidney. Numbers indicate the sequence of events. A_1-receptor, adenosine$_1$-receptor.

Kidney International (2014) 86, 1096–1105

SPLIT trial 2015 JAMA

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

紐西蘭

澳洲

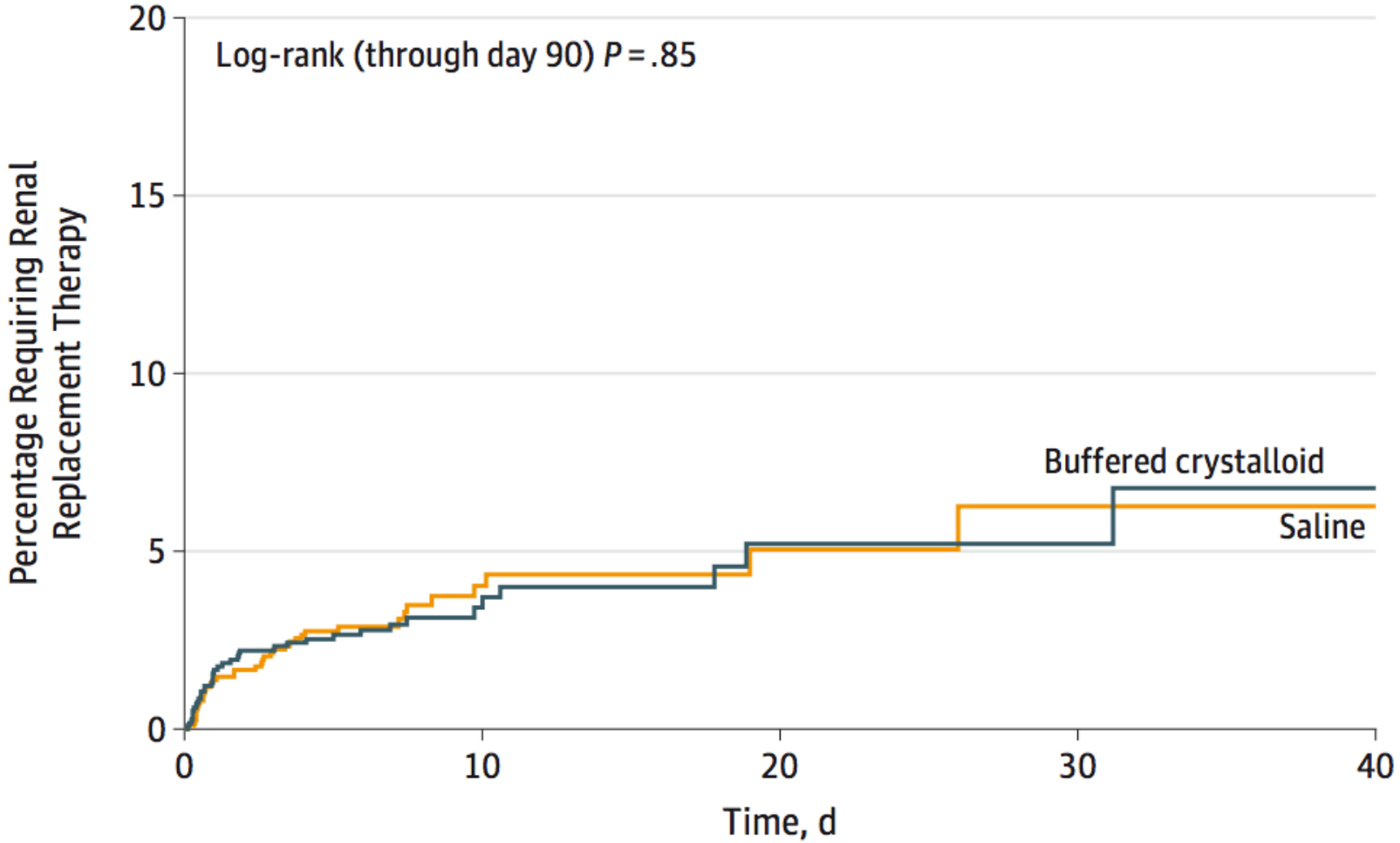
0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy

Primary outcome was the proportion of patients with AKI (RIFLE)

A prospective, investigator initiated, multicenter, blinded, cluster-randomized, double crossover study conducted in 4 tertiary ICUs in New Zealand

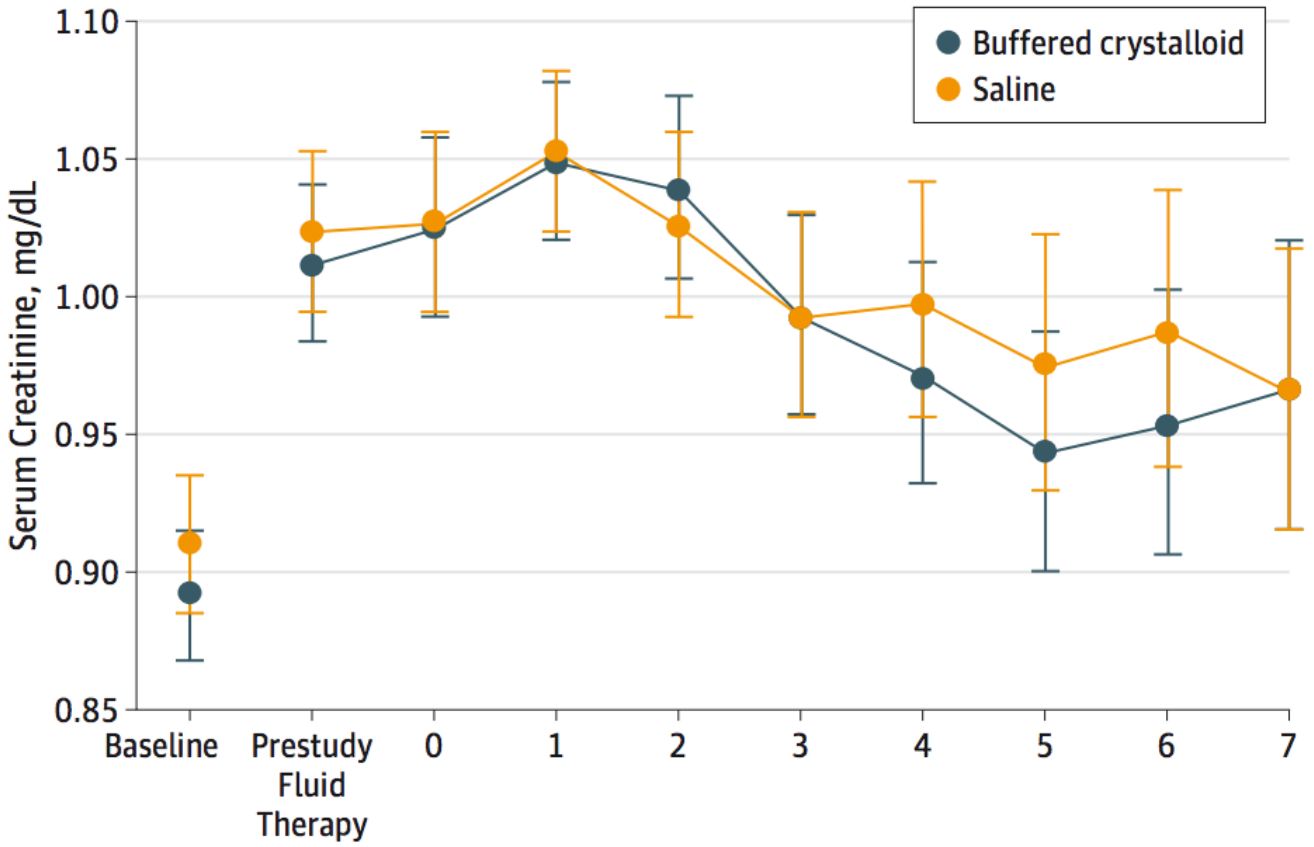
JAMA. 2015;314(16):1701-1710. doi:10.1001/jama.2015.12334

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial



No. at risk					
Buffered crystalloid	1152	341	134	62	36
Saline	1110	310	124	64	28

Figure 4. Daily Serum Creatinine for the Buffered Crystalloid vs Saline Groups[a]



No. of patients										
Saline	1092	820	503	947	442	272	184	135	110	100
Buffered crystalloid	1133	847	481	992	478	297	200	144	112	94

Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI

SMART trial 2018 NEJM

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

A pragmatic, cluster-randomized, multiple-crossover trial conducted in five intensive care units at an academic center

Primary outcome: Major adverse kidney event within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction

N Engl J Med 2018;378:829-39.

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N = 7942)	Saline (N = 7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		

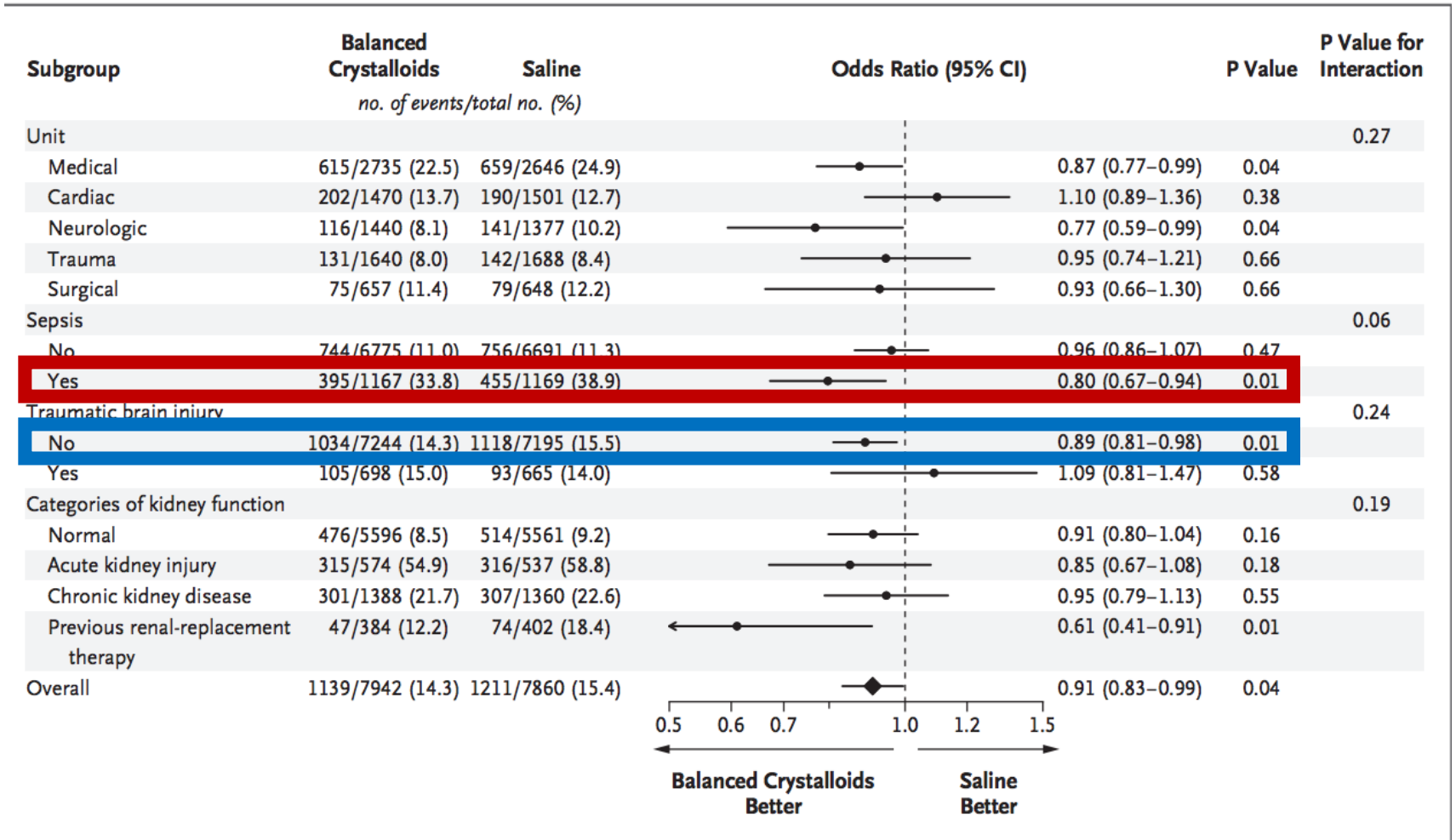
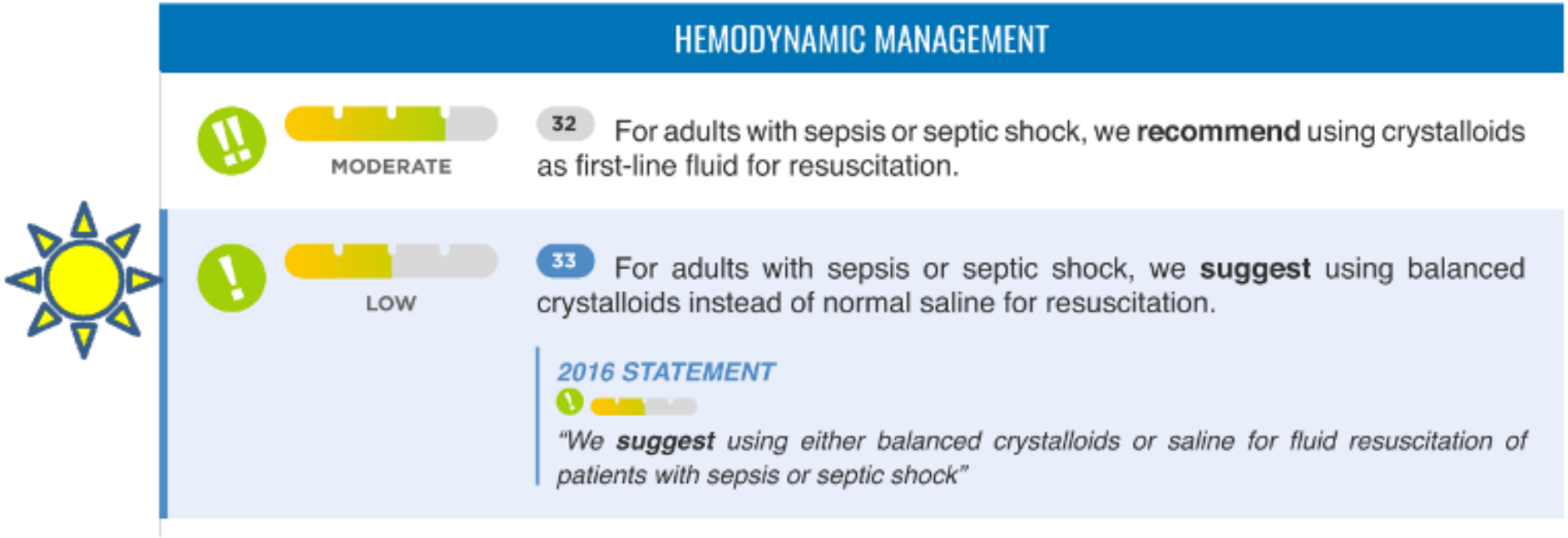


Figure 3. Subgroup Analysis of Rates for the Composite Outcome of Death, New Receipt of Renal-Replacement Therapy, or Persistent Renal Dysfunction.

2021 Sepsis Guideline



「我們建議在敗血症或敗血性休克病人中，
以『平衡型晶體液（**balanced crystalloids**）』作為初始復甦與後續血管內容積補充的首選，而非使用 **0.9%** 氯化鈉（生理食鹽水）。」

BaSICS Trial (JAMA 2021)

90 天死亡率無顯著差異 (26.4% vs 27.2%)；AKI 率相似。
亞組中敗血症/休克病人可能略有益處。

JAMA Network™

QUESTION Among patients in the ICU requiring intravenous fluid challenges, does the use of a balanced solution compared with saline solution (0.9% sodium chloride) improve 90-day survival?

CONCLUSION Among critically ill patients requiring fluid challenges, treatment with a balanced solution compared with saline solution did not significantly reduce 90-day mortality.

POPULATION

5865 Men 4655 Women

ICU patients with ≥1 risk factor for worse outcomes who required fluid expansion and were expected to stay >24 hours

Mean age: 61 years

LOCATIONS

75
ICUs in Brazil

INTERVENTION

11 052 Patients randomized
10 520 Patients analyzed

5230 5290

Balanced solution
Isotonic solution of pH 7.4 (infusion rate also randomized and analyzed separately)

Saline solution
0.9% sodium chloride (infusion rate also randomized and analyzed separately)

PRIMARY OUTCOME

90-day survival

FINDINGS

Deaths within 90 days

Balanced solution
1381 of 5230 patients died

Saline solution
1439 of 5290 patients died

Findings were not statistically significant:
Adjusted HR, **0.97** (95% CI, 0.90 to 1.05)

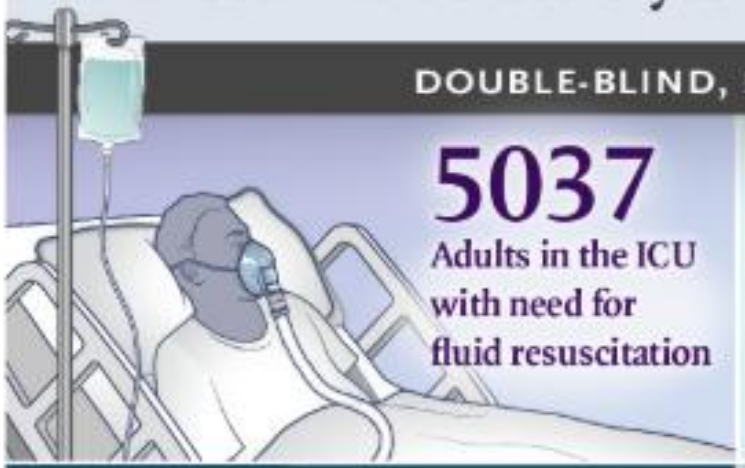
Zampieri FG, Machado FR, Biondi RS, et al; BaSICS investigators and the BRICNet members. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: the BaSICS randomized clinical trial. *JAMA*. Published online August 10, 2021. doi:10.1001/jama.2021.11684

PLUS Trial (NEJM 2022)

90 天死亡率相似 (21.8% vs 22.0%)；
RRT需求、AKI 無差異

The NEW ENGLAND JOURNAL of MEDICINE

Balanced Multielectrolyte Solution vs. Saline in Critically Ill Adults



DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

5037
Adults in the ICU with need for fluid resuscitation

	Balanced multi-electrolyte solution (N=2515)	Saline (N=2522)
Death from any cause at day 90	21.8%	22.0%
	OR, 0.99; 95% CI, 0.86 to 1.14	
Newly initiated renal-replacement therapy	12.7%	12.9%
	Difference, −0.20 percentage points; 95% CI, −2.96 to 2.56	
Mean maximum increase in serum creatinine	0.41 mg/dl	0.41 mg/dl
	Difference, 0.01 mg/dl; 95% CI, −0.05 to 0.06	

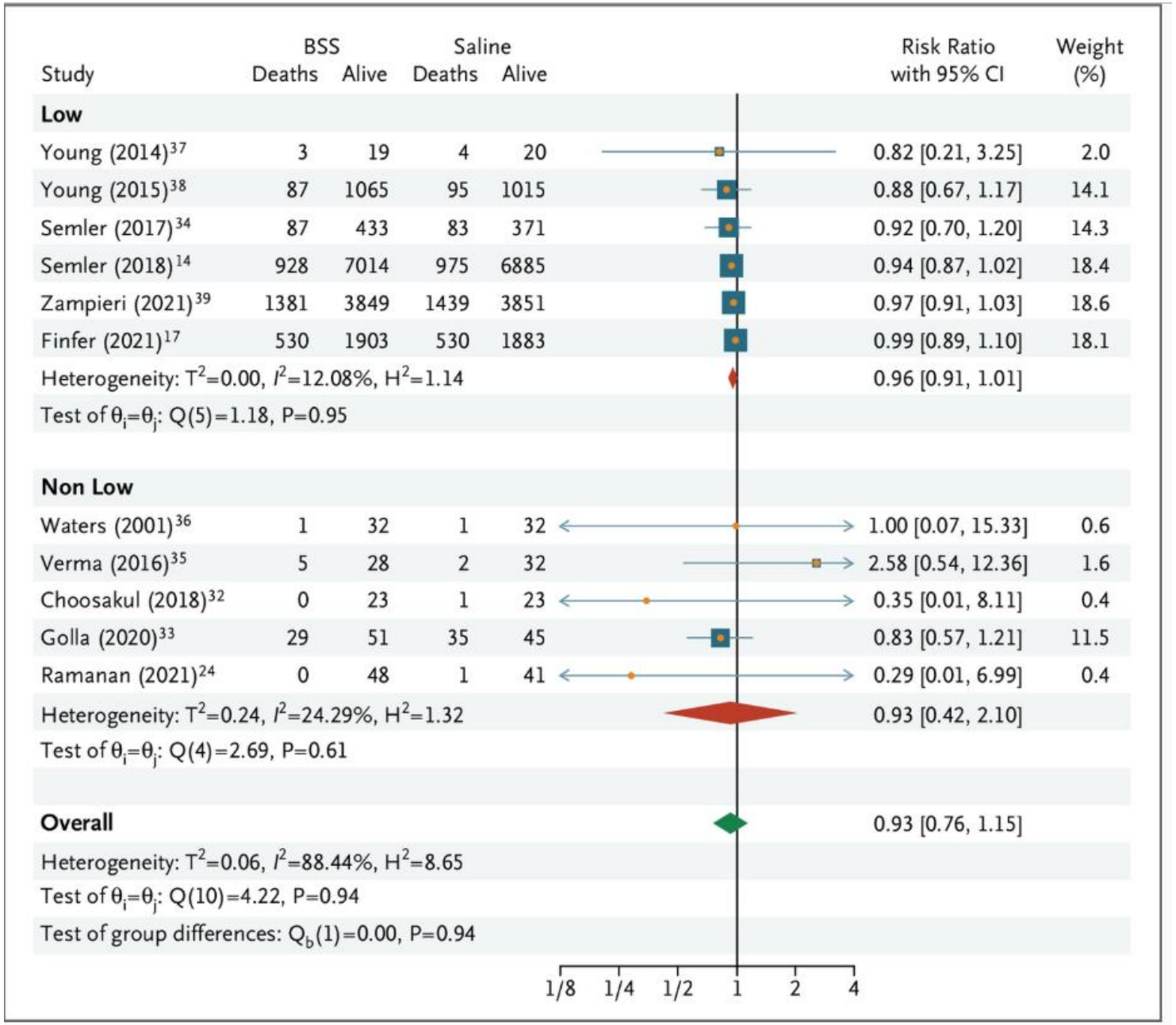
Use of balanced multielectrolyte solution in critically ill adults did not result in a lower risk of death or acute kidney injury than use of saline.

S. Finfer et al. 10.1056/NEJMoa2114464

Evidence for ideal fluid for critical ill patients

	SPLIT 2015	SALT-ED 2018	SMART 2018	BaSICS 2021	PLUS 2022
Design	RCT Double blind 2 crossovers	RCT Non-blinded Pragmatic Multiple crossovers	RCT Non-blinded Pragmatic Multiple crossovers	RCT Double blind No crossover factorial design	RCT Double blind No crossover
Centers	Multi center [4]	Single Center	Single Center	Multi Center [75]	Multi Center [53]
N	2278 65% White	13347 77.5% White	15802 80.4% White	11052	5037
Setting	ICU 70% Surgical	ED/In-patients 18.6% Surgical	ICU 8.2% Surgical	ICU 60.4% Surgical	ICU 44.6% Surgical
Sepsis	4%		14.8%	18.8%	42%
Intervention (Vs Saline)	Plasmalyte 148	Ringer lactate Plasmalyte-A	Ringer lactate Plasmalyte-A	Plasmalyte 148	Plasmalyte 148
IV fluid received per patient	Median 2000ml	Median 1079 ml	2500ml cumulative over 7 days	3600ml cumulative over 7 days	Median 3810ml
Primary outcome	AKI	Hospital free days to D28	MAKE (Persistent creat >200% baseline +new RRT + death) to D30	90 days survival	90 days mortality
Key results	✓ AKI no difference RR 1.04 [0.8, 1.36] ✓ No difference in RRT use, mortality	✓ No difference in hospital free days OR 0.98[0.92,1.04] ✓ Lower MAKE with balanced crystalloid	✓ Lower MAKE with balanced crystalloid OR 0.91 [0.84,0.99] ✓ No difference in mortality, ICU free days, ventilator-free days	✓ No difference in 90 days survival HR 0.97[0.90,1.05] ✓ No difference in AKI, RRT use, ICU stay, mortality	✓ No difference in 90 days mortality 0.15% reduction [-3,.60%, 3.30%] ✓ No difference in RRT use, ICU stay, Ventilator free days

Effect of Balanced Crystalloids Compared with Saline on 90-Day Mortality in Critically Ill Patients by Risk of Bias



NEJM Evidence, 2022;1(2)

重症敗血症液體治療策略：
Balanced Crystalloids 為首選

指引立場

- **Surviving Sepsis Campaign 2021** 建議：
  以平衡型晶體液（Balanced Crystalloids）作為初始與後續補液首選，
  取代 0.9% 生理食鹽水。

臨床效益

- 針對**重症敗血症／休克患者**，
  平衡晶體液可能可以**輕度降低死亡率與急性腎損傷風險**。
- 效果雖有限，但在高輸液量或既有腎功能不全病人中更具臨床意義。

使用考量

- **ICU 創傷腦傷 (TBI)** 病人需評估腦壓，平衡液體**可能有害**。
- 液體選擇應根據**個體化需求**動態調整。

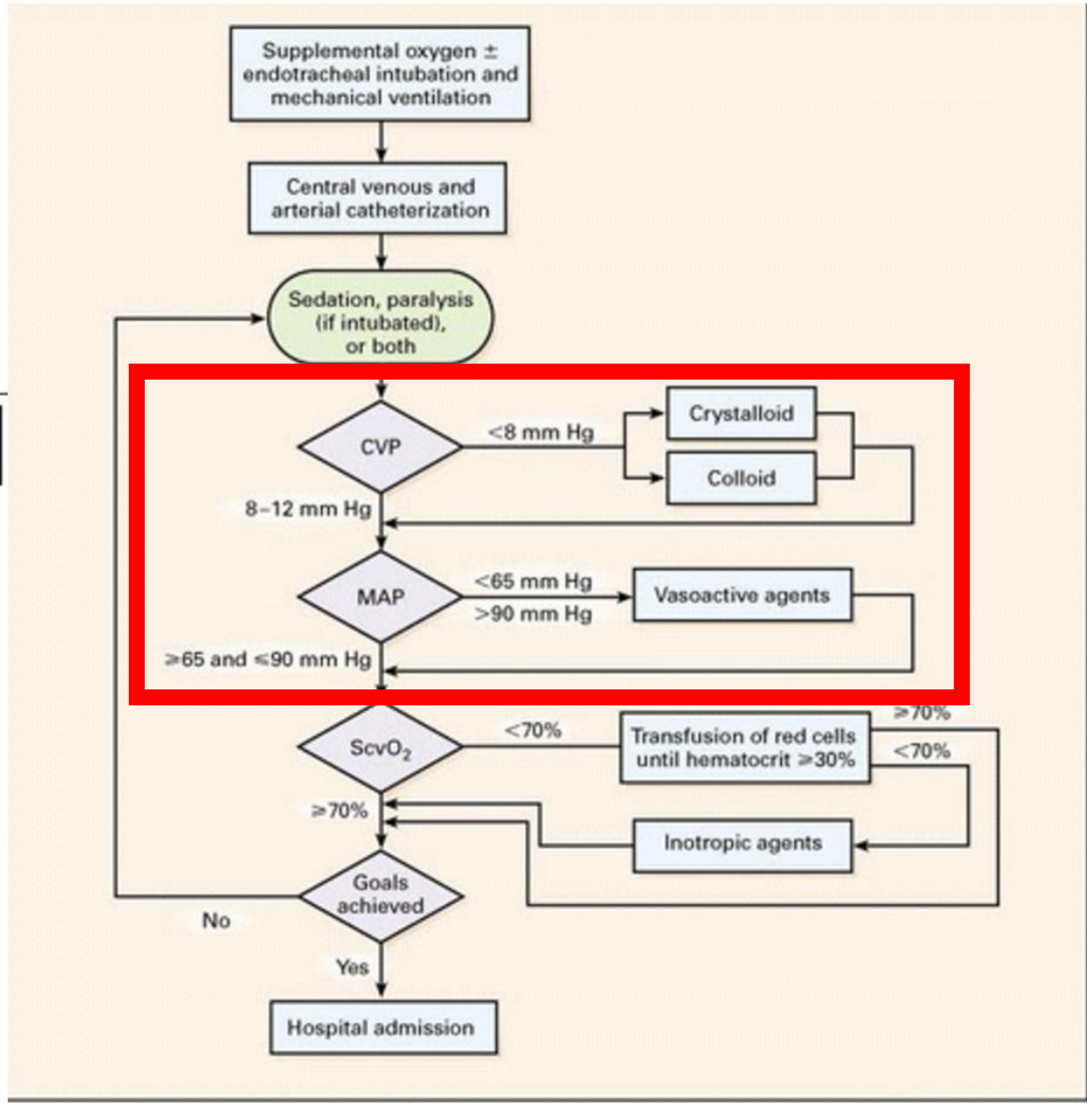
Early vasopressor?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*



Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial

Chairat Permpikul [1], Surat Tongyoo [1], Tanuwong Viarasilpa [1], Thavinee Trainarongsakul [1], Tipa Chakorn [2], and Suthipol Udompanturak [3]

項目	內容
研究對象	成人敗血症併低血壓（經初步液體復甦後 MAP < 65 mmHg）
樣本數	N = 310（早期 NE 組 155 vs 標準治療組 155）
介入措施	早期組：立即給予 NE（0.05 μg/kg/min 起始） + 標準液體治療 對照組：安慰劑輸注 + 醫師自行決定何時啟動 open-label NE
啟動時間（中位數）	早期組 93 分鐘 vs 標準組 192 分鐘（p < 0.001）
主要終點	6 小時內達成休克控制率 （MAP ≥ 65 mmHg 且尿量 ≥ 0.5 mL/kg/hr × 2h 或乳酸下降 ≥10%）
主要結果	早期組 76.1% vs 標準組 48.4%（p < 0.001)
次要結果	- 28 天死亡率：15.5% vs 21.9%（p = 0.15）無顯著差異 - 肺水腫較少（14.4% vs 27.7%，p = 0.004） - 新發心律不整較少（11% vs 20%，p = 0.03）

AJRCCM 2019

Research | Open access | Published: 06 May 2025

Early norepinephrine for patients with septic shock: an updated systematic review and meta-analysis with trial sequential analysis

Rui Shi, Rayan Braïk, Xavier Monnet, Wan-Jie Gu, Gustavo Ospina-Tascon, Chairat Permpikul, Maxime Djebbour, Alice Soumare, Vincent Agaleridis & Christopher Lai

Critical Care **29**, Article number: 182 (2025) | Cite this article

主要結局：(All-cause mortality)

在所有 RCT 中，早期組 vs 晚期組差異**未達顯著** (OR 0.70; 95% CI 0.41-1.19)。

特定亞組分析

在未採取「輸液限制策略」的 2 篇 RCT 中，早期組死亡率**顯著較低** (OR 0.49; 95% CI 0.25-0.96)。

觀察性研究整合

顯示早期啟動與**較低短期死亡率** 有顯著相關 (OR 0.69; 95% CI 0.55-0.86)。

其他結局

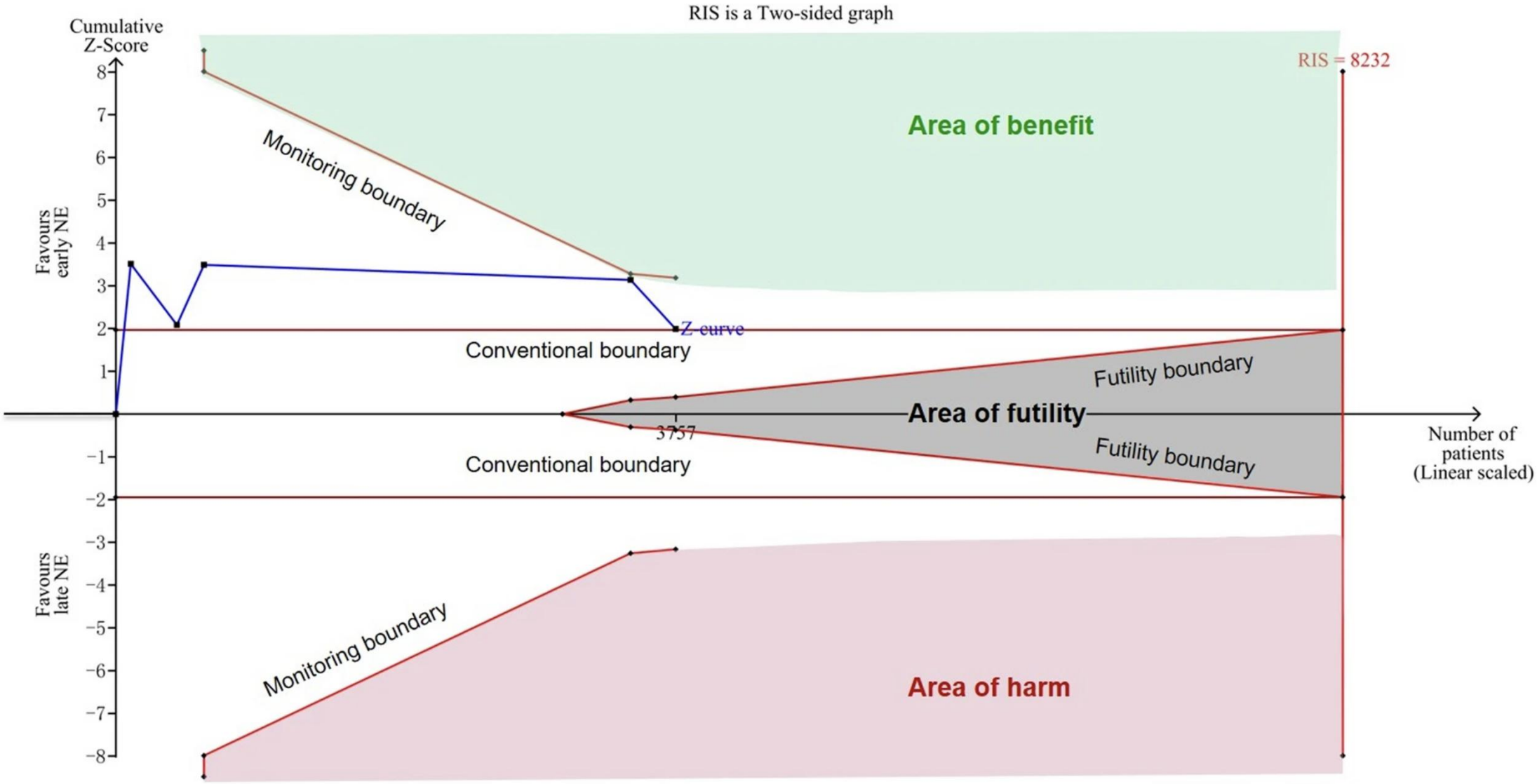
早期組具有：

- 更少輸入液體量
- 更早達到目標 MAP
- 更多「無通氣日」與「ICU 出院日」

Critical Care 2025

Trial Sequential Analysis, TSA

顯示目前累積樣本量尚未達到確定效益的統計界值。



Early vasopressor

- 對於敗血性休克病人，
  早期（於休克診斷或初期液體復甦 1–6 小時內）
  啟動 norepinephrine可能可降低短期死亡率、減少輸液量並加速血壓恢復。

- 然而，根據目前所有 RCT 與 TSA 分析，
  整體證據尚不足以得出確定性結論，
  須透過更大型、嚴謹的隨機試驗以驗證其生存獲益。

Take home message

Crystalloid vs Colloid

- **Balanced crystalloids（平衡型晶體液）為首選：**
  相較 0.9% 生理食鹽水，能減少高氯性酸中毒與腎損傷風險。
- **Colloid 無生存優勢：**
  - HES 增加腎損傷與死亡風險（6S、CHEST Trial）。
  - Albumin 在 ALBIOS trial 中未改善整體死亡率，僅在 septic shock 亞群有潛在益處。

- **臨床應用重點：**晶體液為基礎，albumin 為輔助，避免 HES。

Take home message

Early Vasopressor

1–6 小時內啟動 norepinephrine 可：

- 更快達 MAP ≥ 65 mmHg
- 減少輸液量與肺水腫
- 在部分研究中顯示短期死亡率下降

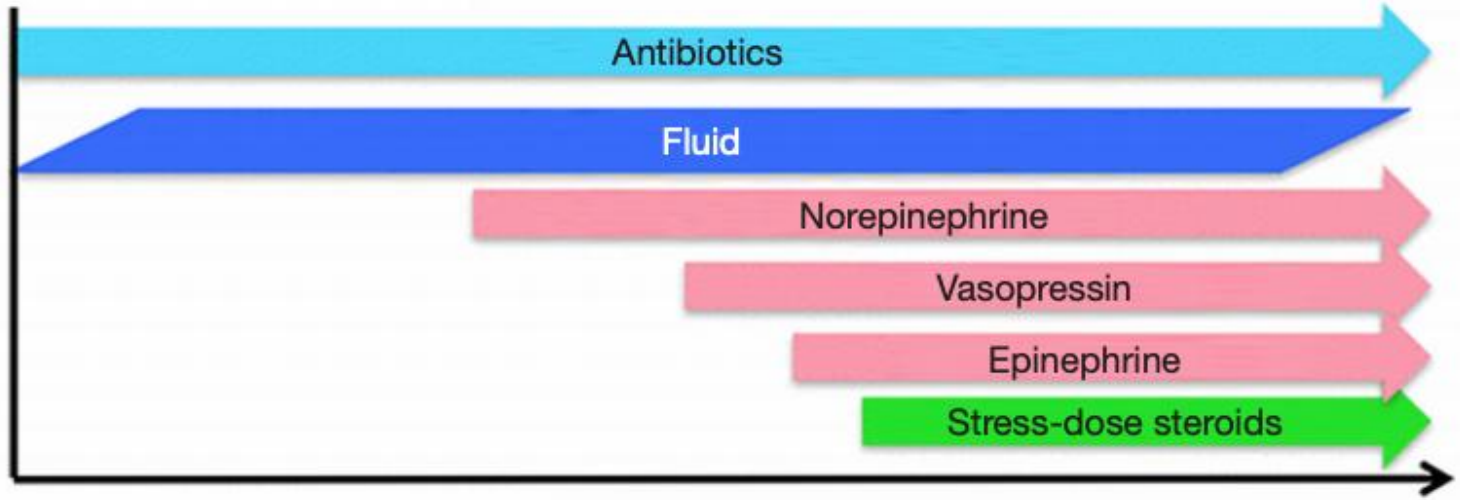
Take home message

SSC 2021 / ESICM 2024

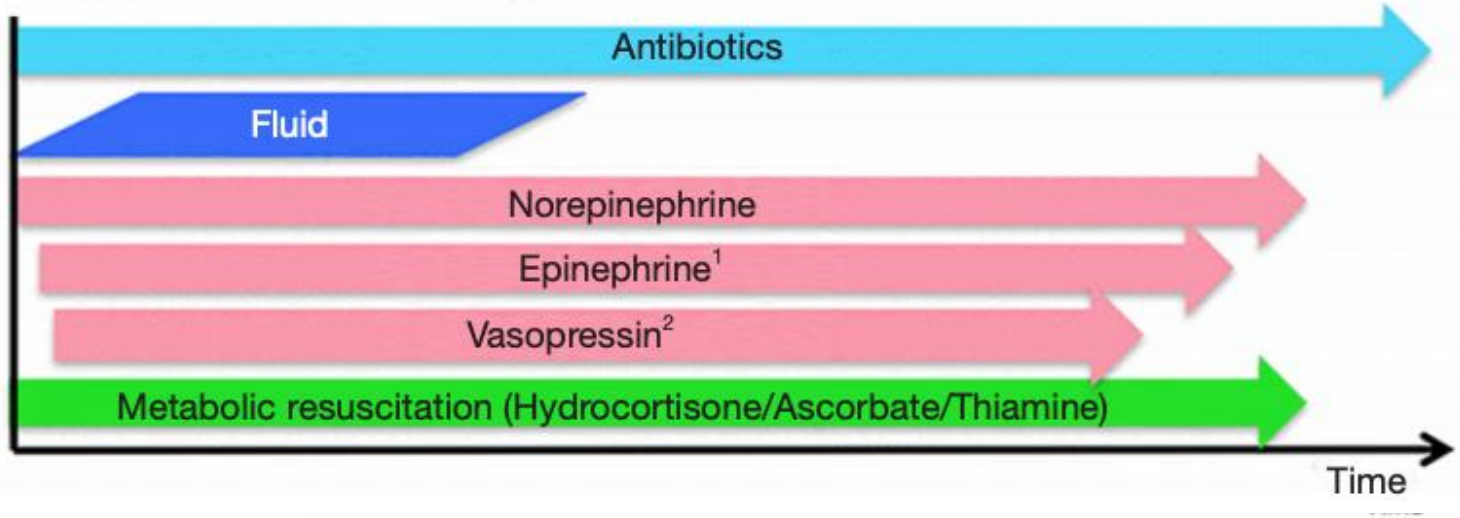
Step 1 ： 初期復甦 → Balanced Crystalloids 30 mL/kg
Step 2 ： 若 MAP < 65 → 早期 Norepinephrine
Step 3 ： 若 NE > 0.5 μg/kg/min → 加 Vasopressin 0.03 U/min
Step 4 ： 若 NE > 1 μg/kg/min → 考慮 Epinephrine 或 Steroid

「少一點鹽水，早一點升壓」

Traditional approach



Revised approach



Paul E Marik. PMID: 31632800
(Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA, USA.)
J Thorac Dis. 2019 Sep;11(Suppl 15):S1969-S1972