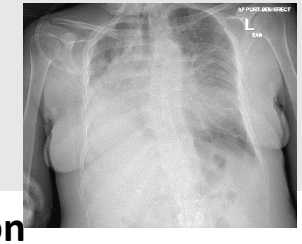
Spreading Knowledge – Improving Outcomes

De-resuscitation & De-treatment in Sepsis & Septic Shock

Case Presentation

32-year-old female with PMH of severe asthma, ulcerative colitis and status post colectomy, and on chronic immunosuppression agents ,who presented with increasing shortness of breath, dry cough and fever. Patient was diagnosed with pneumonia and septic shock that required intubation and multiple bronchoscopies for right lower lobe atelectasis and mucus plugging.

Hemodynamics
BP 86/30
HR 119/min
LA 3.4



Organ Functions
PF ratio : 165
Creatinine 1.6
PLATS: 120K

IV Antibiotics
Ceftriaxone, azithromycin and Vancomycin
Procalcitonin was 3.87

Resuscitation
30 mL/kg IV bolus followed by intermittent boluses and IVF maintenance

Vasopressors
Norepinephrine up to 0.5 mcg/kg/min and Vasopressin

Steroid Therapy
Hydrocortisone 50 mg every 6 hours

4 days later

No organism is cultured
MRSA screen is negative
Vancomycin was stopped
Procalcitonin was 0.7

Fluid balance was positive for 8.7 Liters since admission
IAP 15 cm H2O
IVC 2.3 cm
50% pulsatality in portal vein

Lactic acid improved to 1.7 and norepinephrine was weaned down to 0.12 mcg/kg/min
Vasopressin was continued

Remained on steroid therapy

What would your approach be for this patient? (check all what apply)?

- ❑ Start diuresis and aim for negative fluid balance
- ❑ Wean norepinephrine first before stopping vasopressin
- ❑ Stop antibiotics once procalcitonin is down by 80%
- ❑ Discontinue hydrocortisone without tapering once off the vasopressors

Questions?

When should we start fluid de-resuscitation?

How should vasopressors be discontinued?

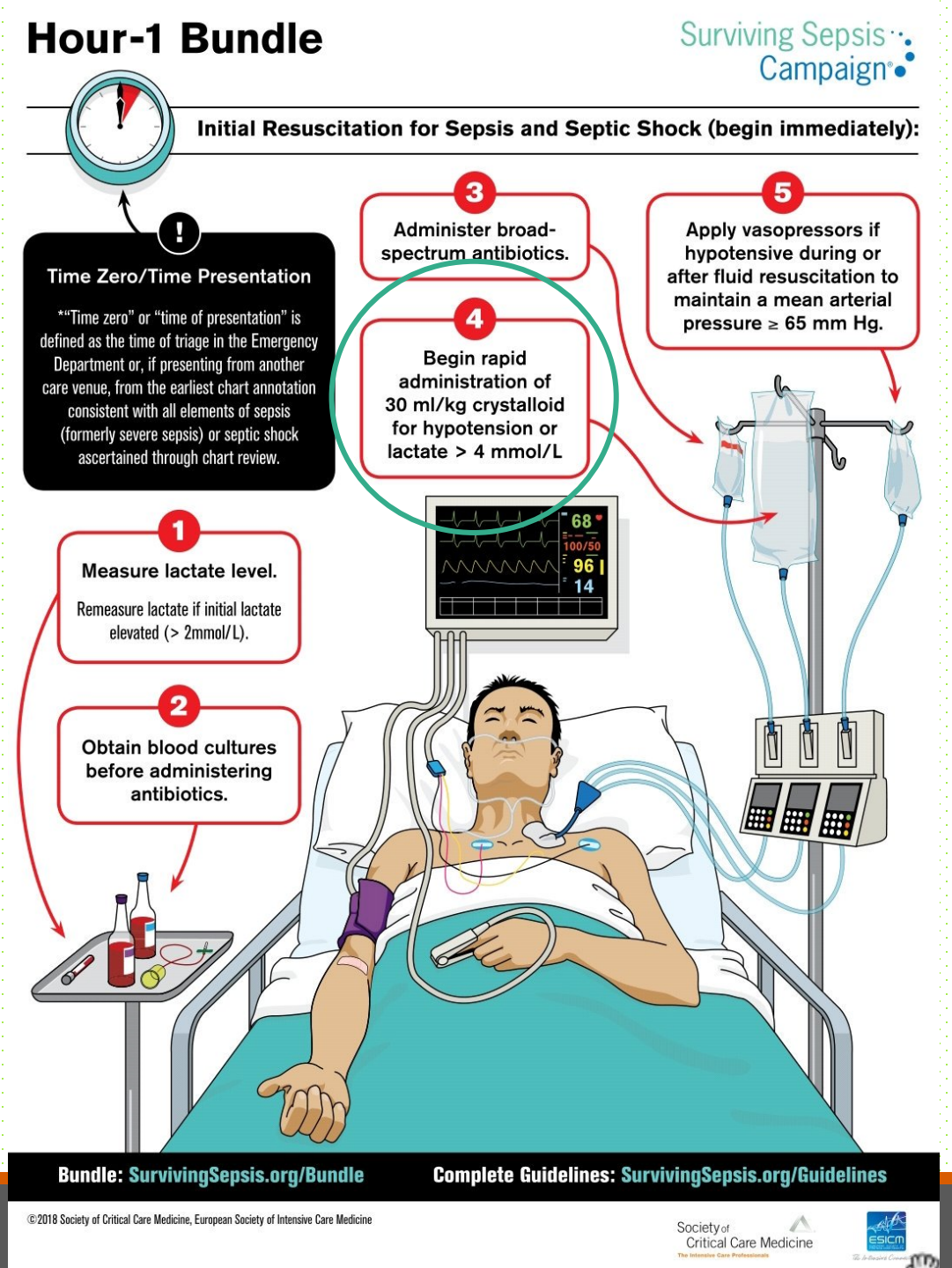
Should we tapper or discontinue steroids?

Can we guide antibiotic discontinuation based on procalcitonin?

Septic Patients Resuscitated with Fluid

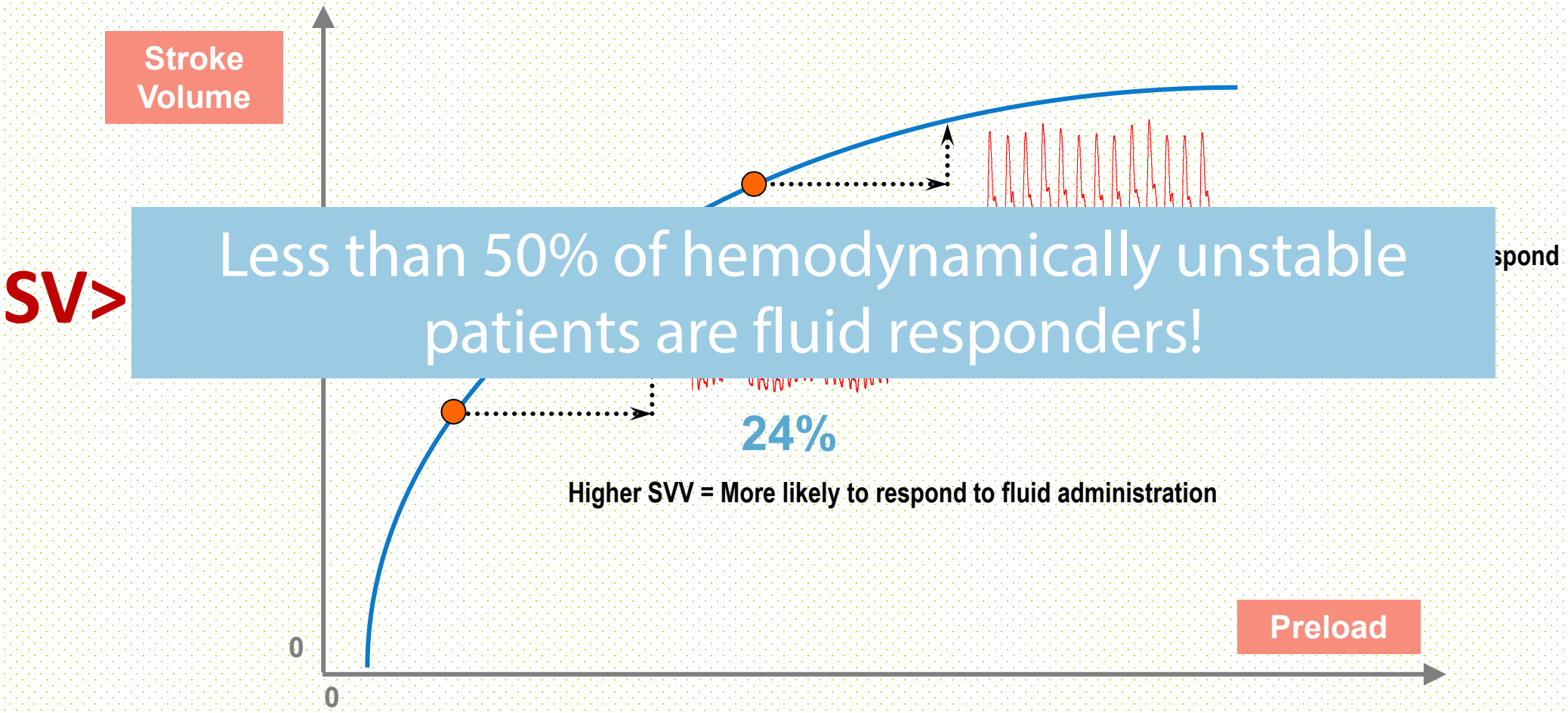
Sepsis is associated with generalized endothelial injury and capillary leak and has traditionally been treated with large volume fluid resuscitation. Some patients with sepsis will accumulate bodily fluids.

What is the association between a positive fluid balance/fluid overload and outcomes in critically ill adults, and do interventions aimed at reducing fluid balance lead to improved outcomes?



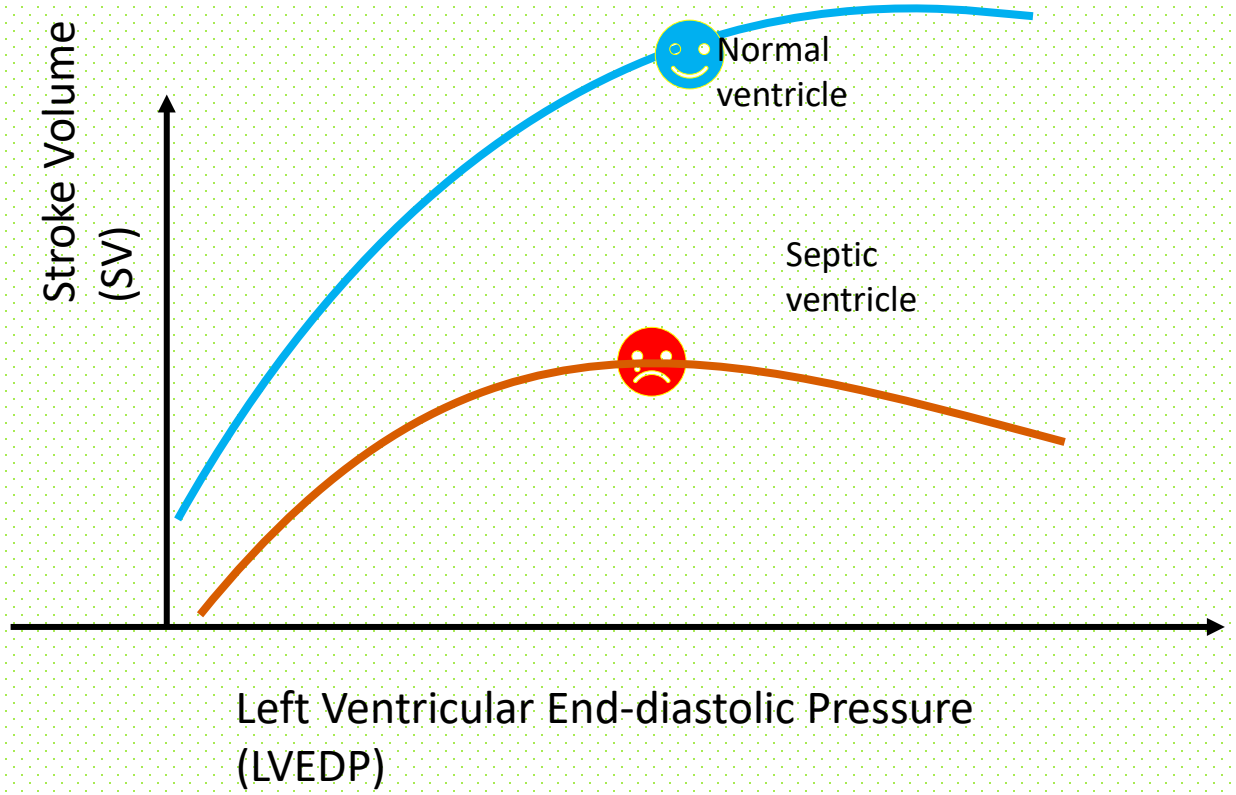
Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018 Jun;44(6):925-928.

SVV to Help Clinicians Optimize Preload / Cardiac Output



Rise in Stroke Volume by >10% has been widely accepted as an indicator of adequate response to fluid resuscitation.

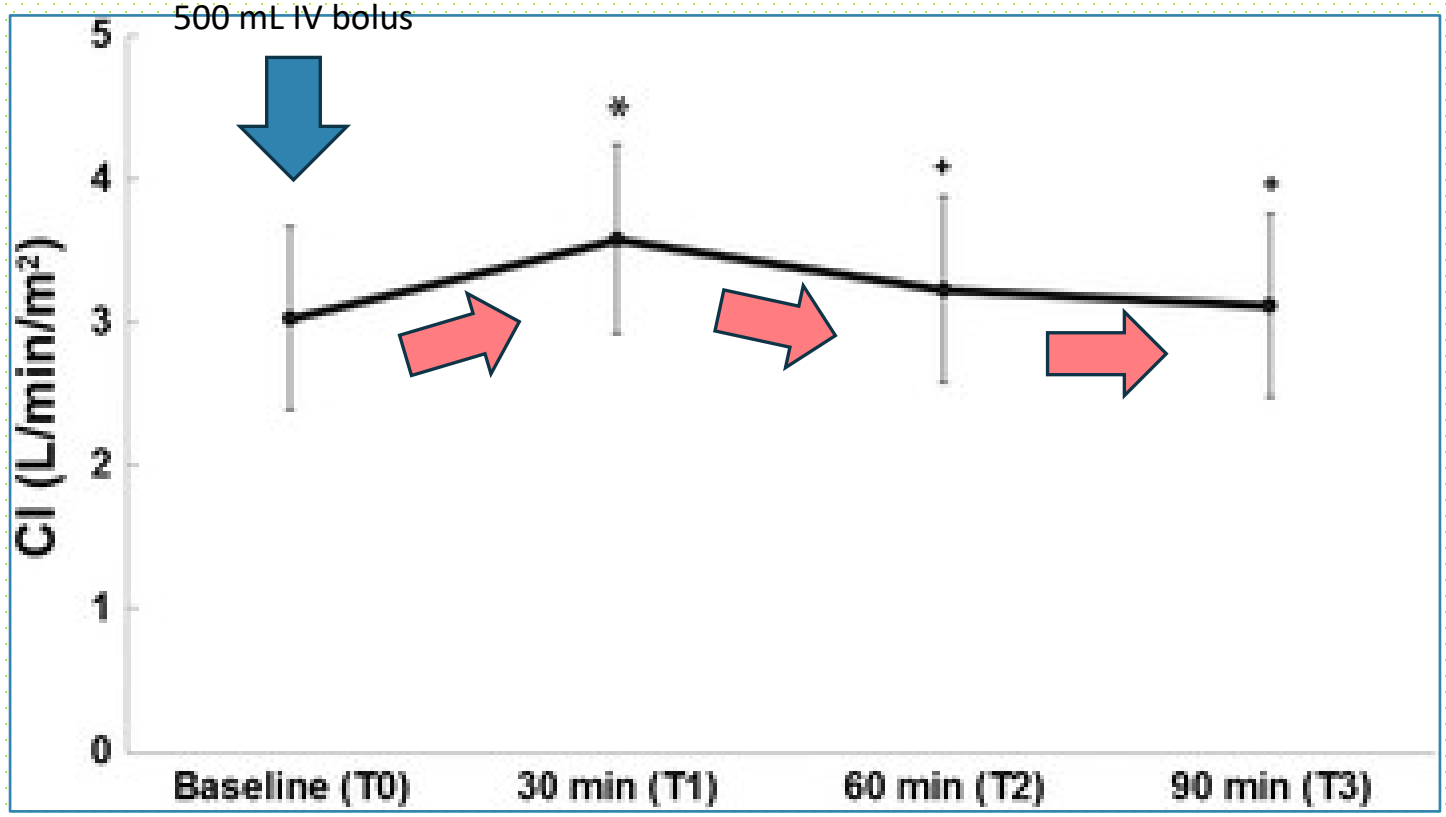
Frank-Starling Curve in Septic Patients



In patients with sepsis the Frank-Starling (or cardiac function curve) is shifted downwards and to the right, with the septic heart showing a limited response to fluid loading.

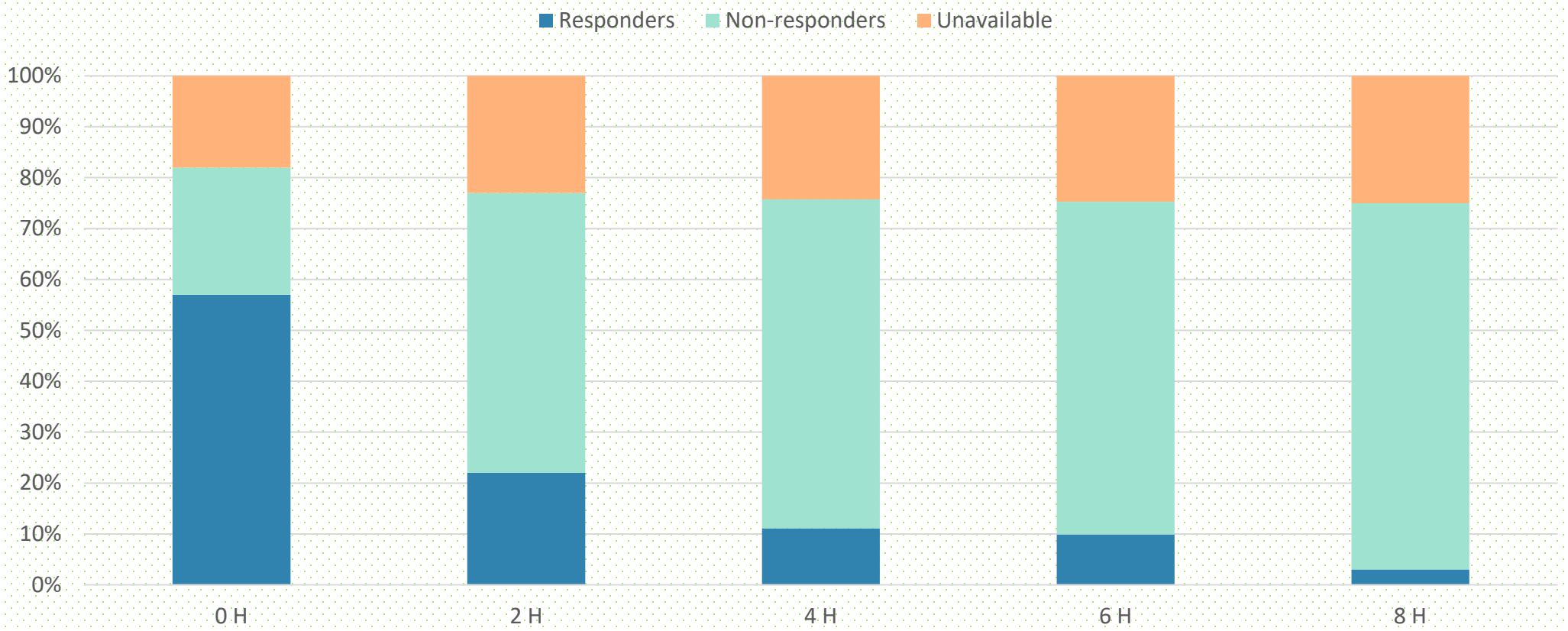
Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation

20 critically ill patients with 500 mL IV bolus



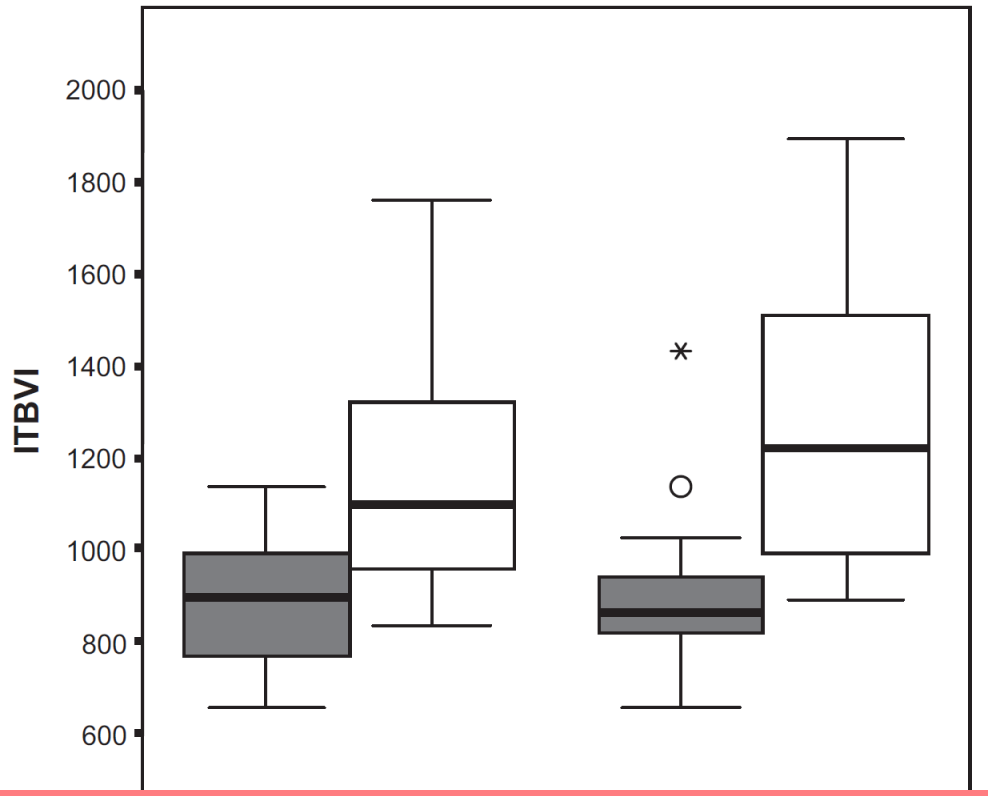
Nunes TS, et al. Ann Intensive Care. 2014 Aug 1;4:25.

Fluid Responsiveness over time in Patients with Septic Shock



Those patients who were initially fluid responders rapidly become non-responsive to fluid challenges

Hernández G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA* 2019;321:654-64

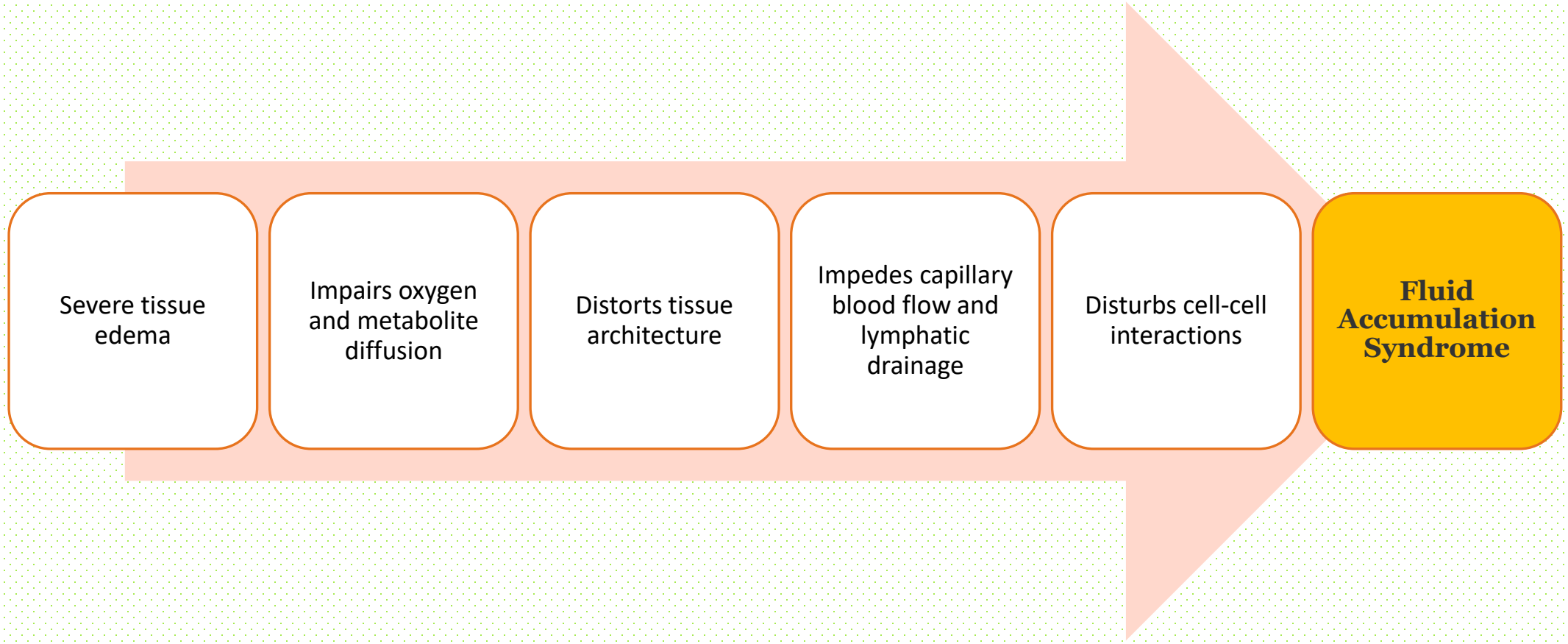


In critically ill patients with endothelial injury and leaky capillaries, less than 5% of a fluid bolus remains intravascular after 90 minutes.

loading. In those patients who received fluid loading, the ITBVI (intrathoracic blood volume index) increased significantly in the control group patients; however, this effect did not happen in the septic group.

Sanchez M, Jimenez-Lendinez M, Cidoncha M et al. Anaesth Intensive Care 2011; 39: 1022–1029.

Large volume fluid resuscitation results in:



Marik PE: Iatrogenic salt water drowning and the hazards of a high central venous pressure. Ann Intensive Care 2014; 4: 21

Fluid Accumulation Syndrome

Abdominal wall
- ↑Tissue edema
- Impaired lymphatic drainage
- ↑Poor wound healing
- ↑Wound infection
- ↑Pressure ulcers
- ↓Abdominal compliance

Respiratory
- ↑Pulmonary edema
- ↑Pleural effusion
- Altered pulmonary and chest wall elastance
- Alteration in gas exchange
- ↑Extravascular lung water
- ↓Lung volumes
- ↑WOB
- Difficult weaning

Renal
- Interstitial edema
- ↑Venous pressure
- ↓Renal blood flow
- ↑Interstitial pressure
- ↑Salt + water retention
- ↑Uremia, ↓GFR, ↑RVR
- Renal compartment syndrome

Cardiovascular
- ↑Myocardial edema
- Conduction disturbance
- Impaired contractility
- Diastolic dysfunction
- ↑CVP and PAOP
- ↓Venous return
- ↓SV and CO
- ↑Pericardial effusion
- ↓GEF, ↑GEDVI, ↑CARS

Hepatic
- ↑Hepatic congestion
- Impaired synthetic function
- ↑Cholestasis
- ↓Cytochrome P450 activity
- Hepatic compartment syndrome

Gastrointestinal/visceral
- ↑Ascites formation
- ↑Gut edema
- ↑Malabsorption
- ↓Bowel contractility (ileus)
- ↑ IAP, ↓APP and ACS
- ↑Intestinal permeability
- ↓Splanchnic flow
- ↑Bacterial translocation

CNS
- Cerebral edema
- Impaired cognition
- ↑Delirium
- ↑ICP, ↓CPP, ↑IOP
- ICH
- Intracranial compartment syndrome (ICS)
- Ocular compartment syndrome (OCS)

Fluid accumulation syndrome (FAS) describes the presence of any % of fluid accumulation or fluid overload with negative impact on end-organ function

Global Increased Permeability Syndrome (GIPS)

- High capillary leak index (CLI>60, expressed as the ratio of CRP over albumin)
- Excess interstitial fluid
- Persistent high extravascular lung water index (EVLWI)
- No late conservative fluid management (LCFM) achievement
- Progression to organ failure

Polycompartment syndrome

- Two or more anatomical compartments have elevated compartmental pressures
- Capillary leak and impaired flow phase
- Head, chest, abdomen, and extremities: mainly encapsulated organs (brain, kidneys, and liver).

The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock

Claire V. Murphy, PharmD; Garrett E. Schramm, PharmD; Joshua A. Doherty, BS; Richard M. Reichley, RPh; Ognjen Gajic, MD, FCCP; Bekele Afessa, MD, FCCP; Scott T. Micek, PharmD; and Marin H. Kollef, MD, FCCP

212 patients with ALI complicating septic shock

Retrospective Analysis

Adequate initial fluid resuscitation (AIFR) was defined as the administration of an initial fluid bolus of >or= 20 mL/kg prior to and achievement of a central venous pressure of >or= 8 mm Hg within 6 h after the onset of therapy with vasopressors. Conservative late fluid management (CLFM) was defined as even-to-negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset.

Murphy CV, Kollef MH et al. Chest. 2009 Jul;136(1):102-109.

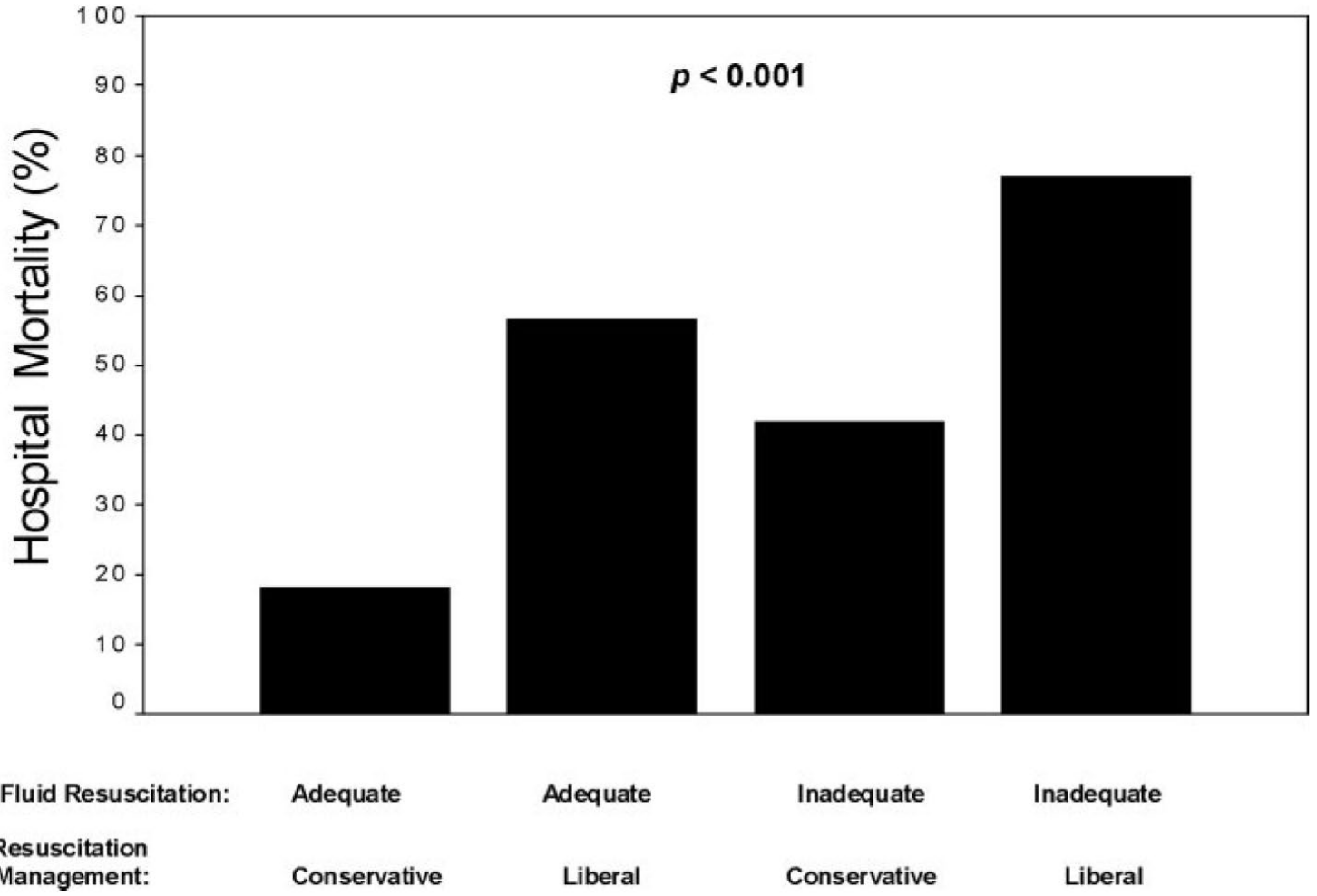


FIGURE 3. Hospital mortality according to whether or not patients achieved AIFR, CLFM, both, or neither.

ICU
MANAGEMENT & PRACTICE

ICU Volume 12 - Issue 2 - Summer 2012 - Series

Fluid Overload is Not Only of Cosmetic Concern

Does a management strategy attempting to obtain a daily fluid balance (FB) close to zero, or even negative (conservative fluid strategy), after day three result in a lower intra-abdominal pressure (IAP) and improved patient outcome compared with management approach that accept a liberal fluid strategy, and will the latter result in higher IAPs in critically ill adults in intensive care units?

Malbrain MLNG, Cordemans C, Van Regenmortel N: Fluid overload is not only of cosmetic concern (Part II): Results from a meta-analysis and practical approach. ICU Management 2012; 12: 34–37.

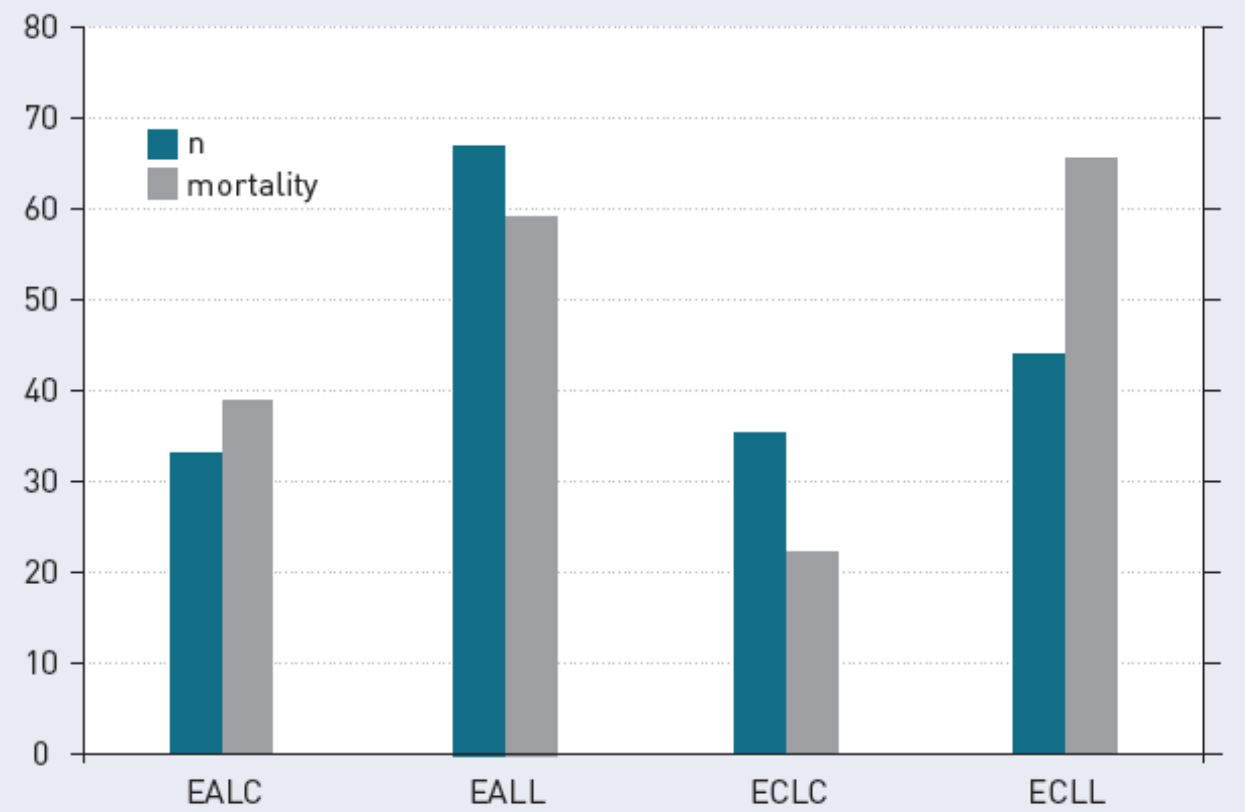


Figure 2. Bar graph showing patient distribution and outcome in different fluid management categories.

Malbrain MLNG, Cordemans C, Van Regenmortel N: Fluid overload is not only of cosmetic concern (Part II): Results from a meta-analysis and practical approach. ICU Management 2012; 12: 34–37.

Fluid Stewardship

4 Indications

- Resuscitation
- Maintenance
- Replacement
- Nutrition

4 Phases (ROSE model)

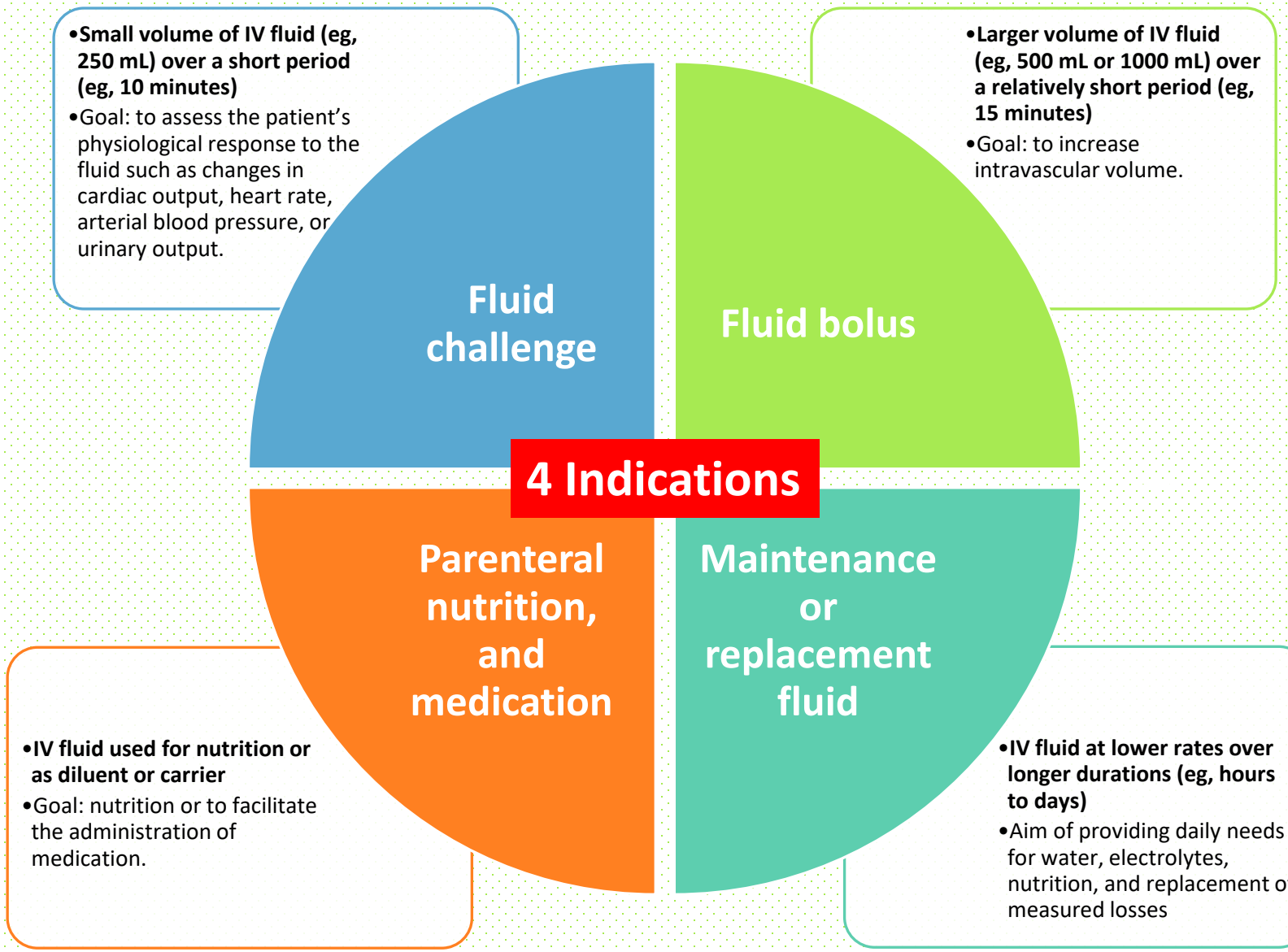
- Resuscitation
- Optimization
- Stabilization
- Evacuation

4 D's

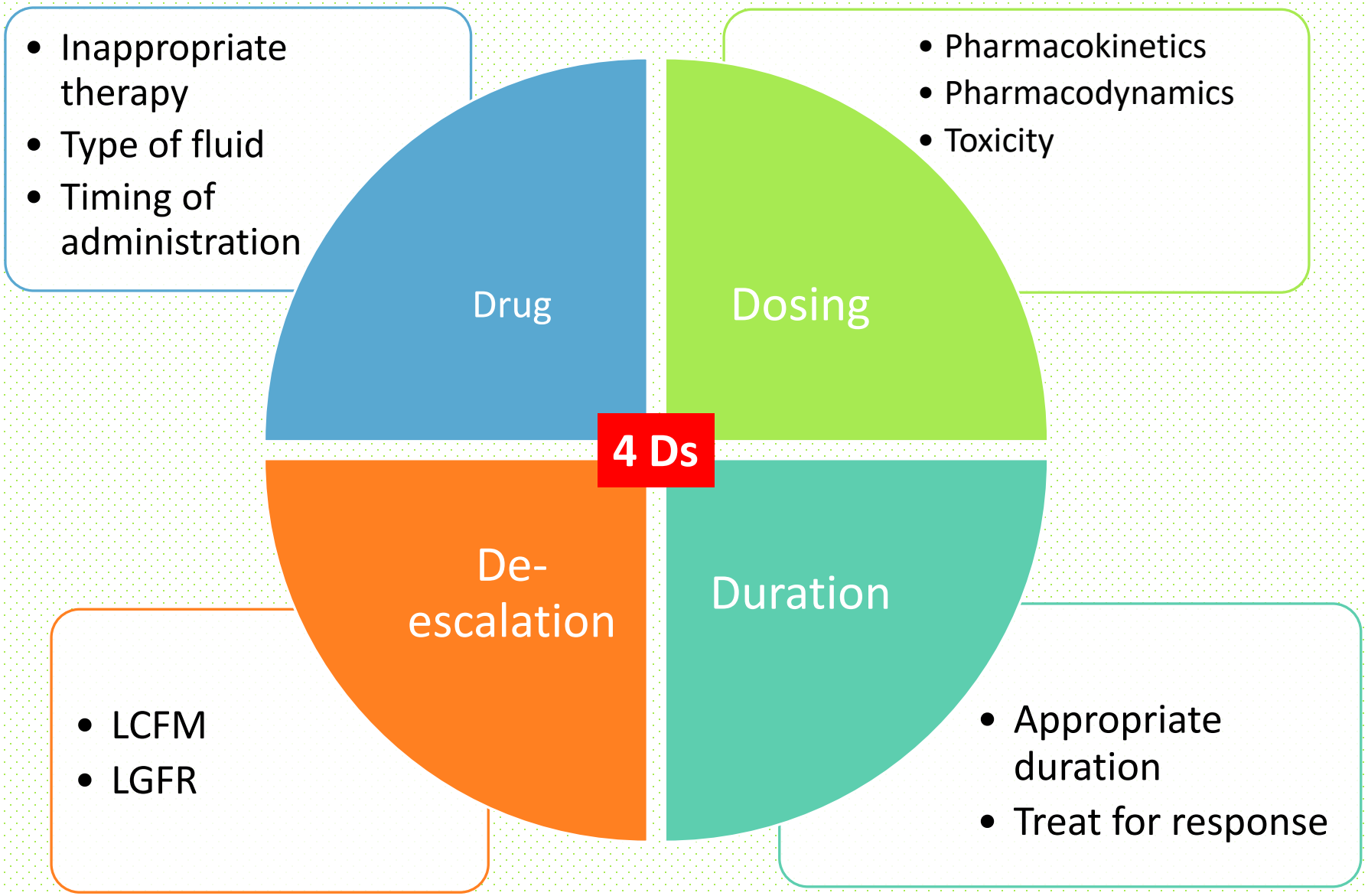
- Drug
- Dose
- Duration
- De-escalation

4 Questions

- When to start fluid therapy
- When to stop fluid therapy
- When to start fluid removal
- When to stop fluid removal



Zampieri FG, Bagshaw SM, Semler MW. Fluid Therapy for Critically Ill Adults With Sepsis: A Review. *JAMA.* 2023;329(22):1967–1980



Malbrain, M.L.N.G., Van Regenmortel, N., Saugel, B. *et al.* Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. *Ann. Intensive Care* **8**, 66 (2018)

ROSE Model

Resuscitation

Early adequate fluid management (reverse hypoperfusion)

Administer initial fluid boluses (i.e. 30 ml/kg/1hour or a mini bolus 4ml/kg in 5-10 minutes)

Vasopressors if necessary

Assess responsiveness to fluid

Optimization

Establish perfusion and organ rescue

Fluid based on responsiveness and avoid fluid overload

Titrate vasopressors for specific hemodynamic targets

Aim for neutral balance

Stabilization

Maintain perfusion and organ support

Late conservative fluid management

Monitor for fluid overload and any organ dysfunction

Two consecutive negative balance within the 1st week after initial insult

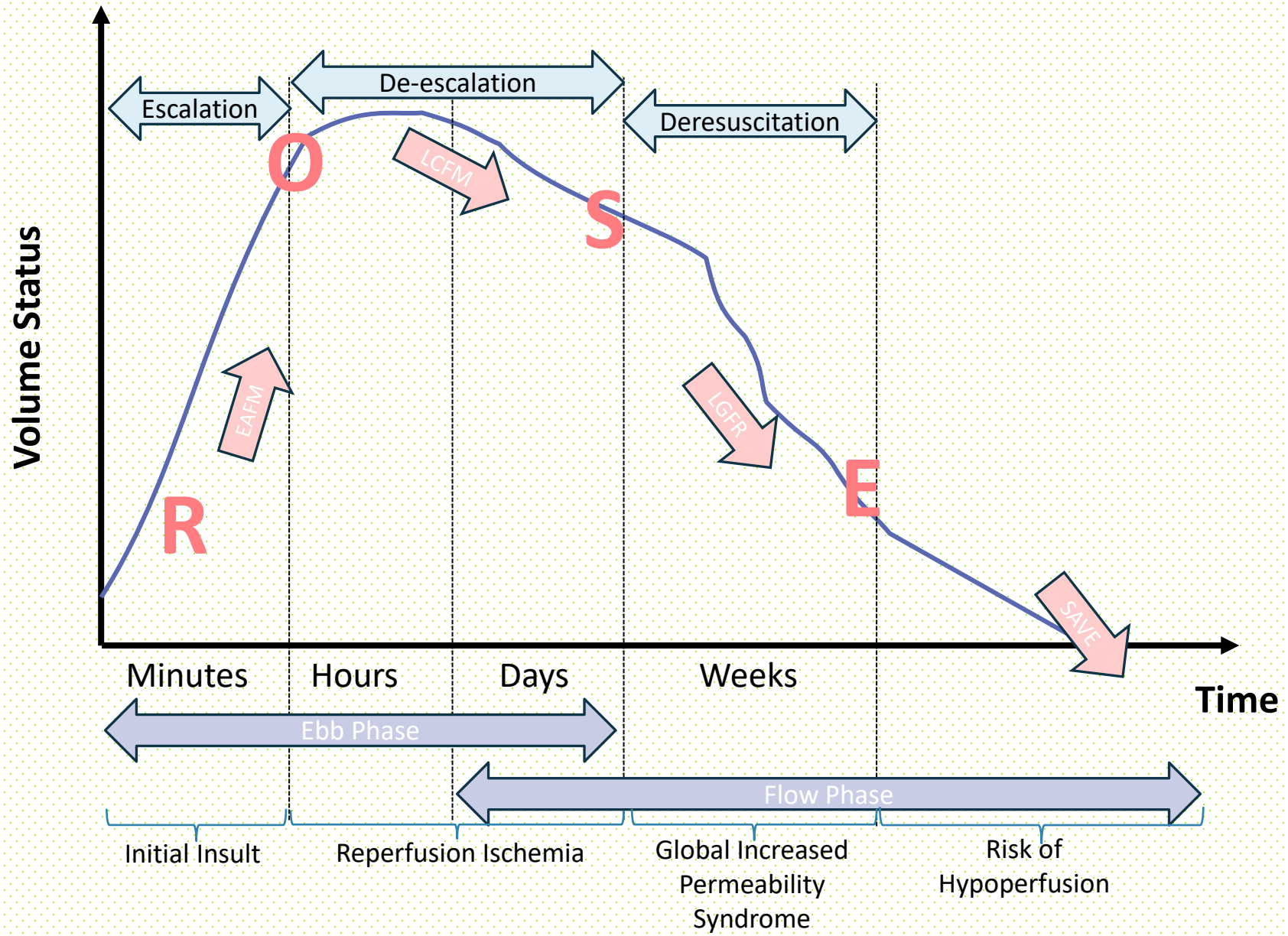
Evacuation

Organ recovery and removal of excess fluid

Resolving fluid overload

Active late goal directed fluid removal and negative FB with diuretics or kidney replacement therapy if indicated

Zampieri FG, Bagshaw SM, Semler MW. Fluid Therapy for Critically Ill Adults With Sepsis: A Review. *JAMA*. 2023;329(22):1967–1980



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

4 Questions

START FLUID

- MAP <65 mmHg
- GEDVI <640ml/m^2
- RVEDVI <80ml/m^2
- CVP <8mmHg or PAOP <10mmHg
- CI <2.5L/min/m^2
- PPV or SVV >12-15%
- Positive PLR test
- Lactate >3mmol/L
- IVCCI >50%

STOP FLUID

- MAP/APP >65/55mmHg
- GEDVI 640-800ml/m^2
- CI >2.5L/min/m^2
- PPV or SVV <12%
- Negative PLR test
- Lactate <2mmol/L
- LVEDAI 8-12cm^2/m^2
- IAP <15mmHg

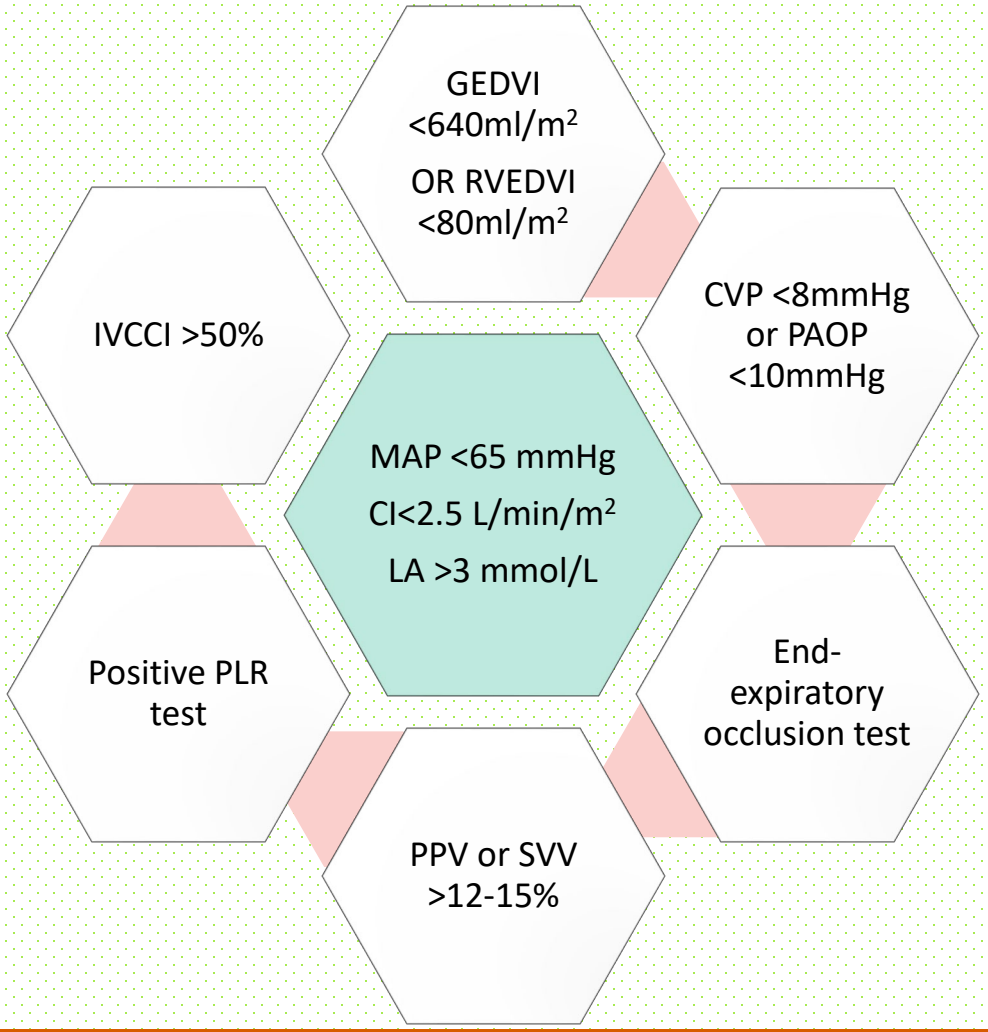
REMOVE FLUID

- MAP/APP>65/55mmHg
- GEDVI >850ml/m^2
- EVLWI >10-12ml/kg PBW
- PVPI >3 and PF ratio <150
- PPV or SVV <12%
- Negative PLR test
- LVEDAI >14cm^2/m^2
- High VExUS score
- IAP >12-15mmHg
- COP <16-18mmHg, CLI >60
- BIA: ECW/ICW>1; V_E>5%

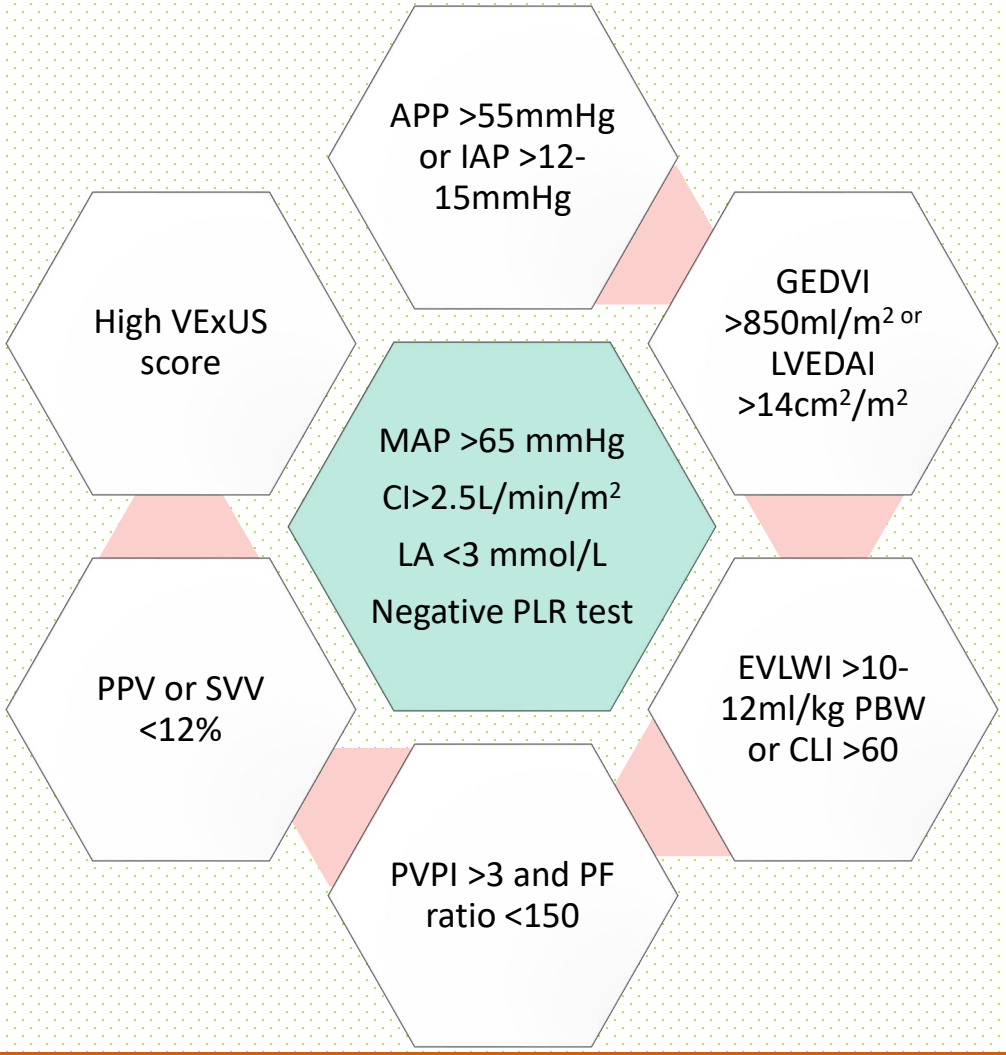
STOP REMOVAL

- MAP/APP <55/45mmHg
- PPV or SVV >15%
- Positive PLR test
- Lactate >2.5mmol/L
- S_vO_2 <70-75%
- $S_{cv}O_2$ <65-70%
- ICG PDR <14-16%

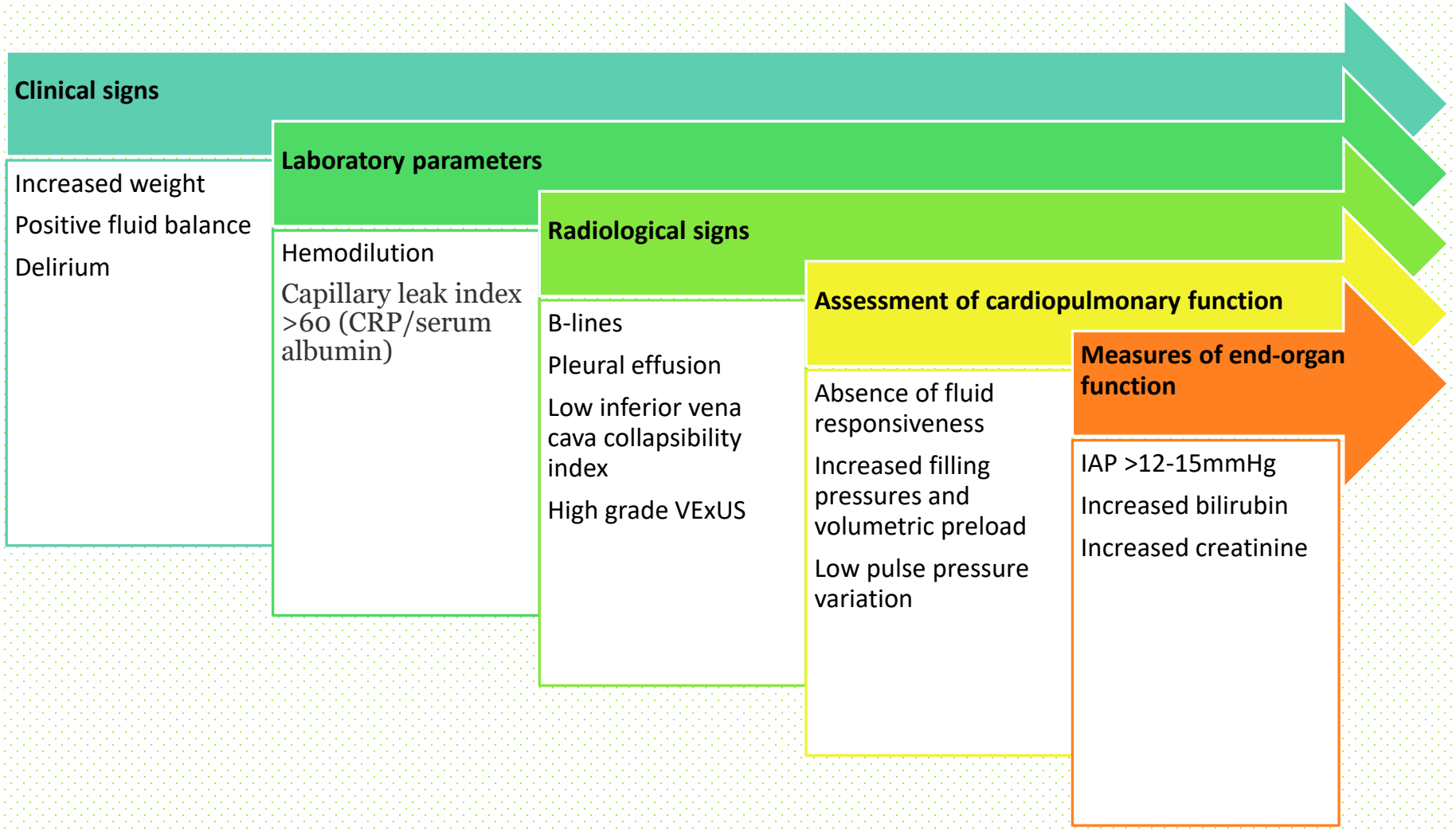
Consider Fluid Boluses



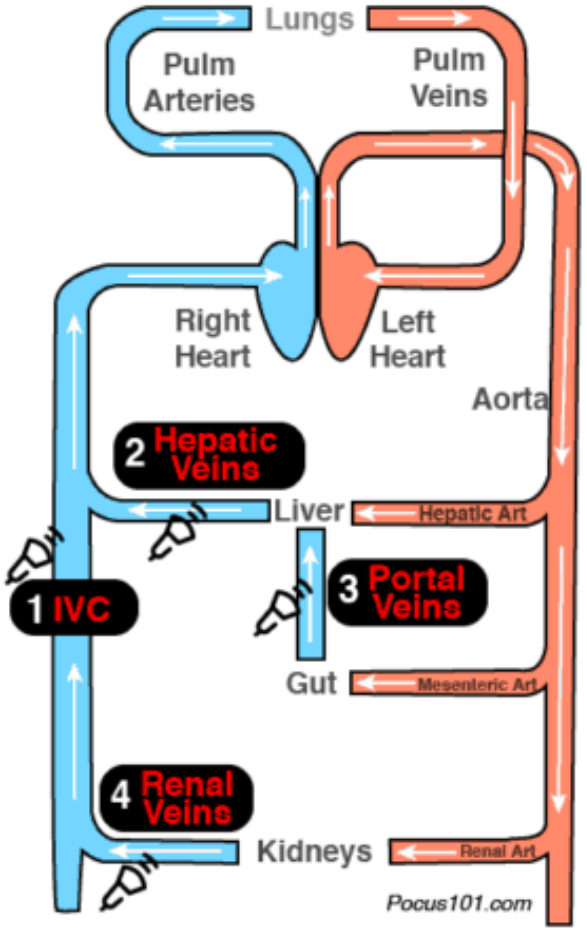
Consider Fluid Removal



Triggers for De-resuscitation

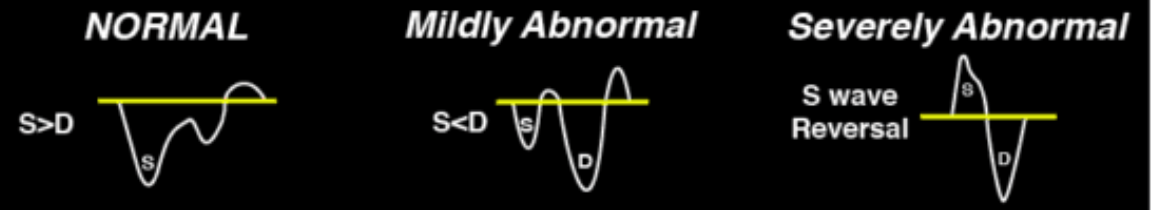


Venous Excess Ultrasound VExUS

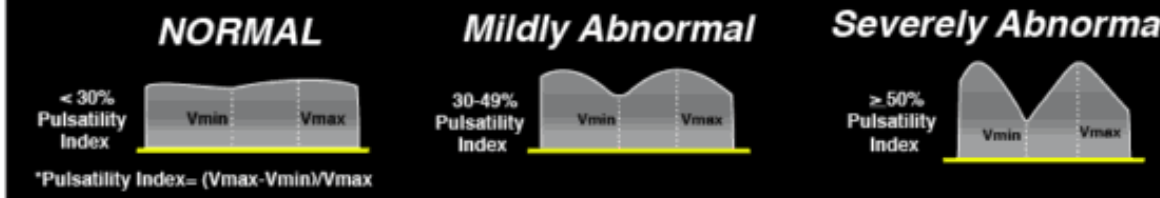


Step 1: IVC Diameter: If ≥2cm, proceed to step 2

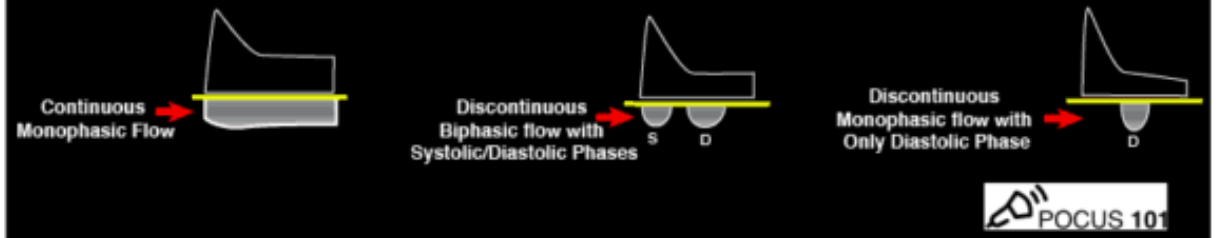
Step 2: Hepatic Vein Doppler



Step 3: Portal Vein Doppler



Step 4: Renal Vein Doppler



Interpretation

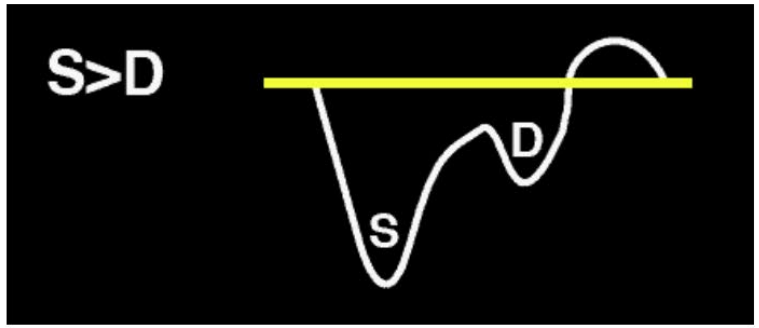
Grade 0
(no congestion)
IVC < 2cm

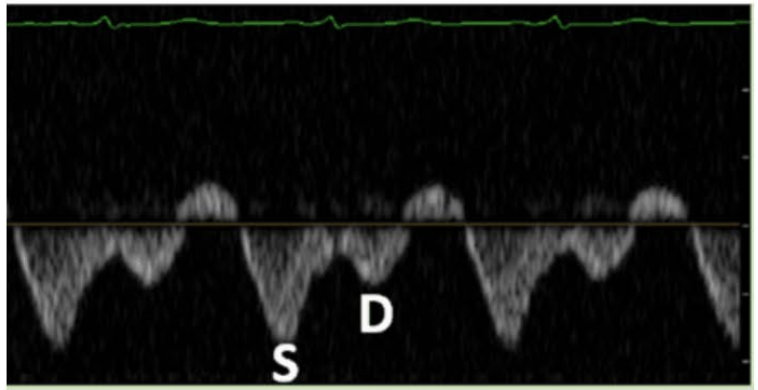
Grade 1
(Mild congestion)
IVC ≥2cm and any combo of Normal or Mildly Abnl Patterns

Grade 2
(Moderate congestion)
IVC ≥2cm and ONE Severely Abnl Pattern

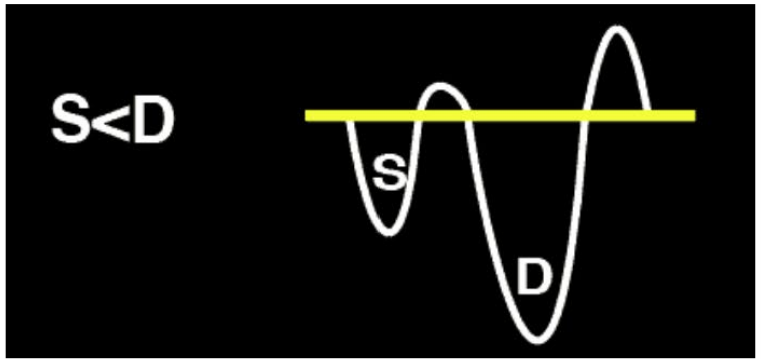
Grade 3
(Severe congestion)
IVC ≥2cm and ≥ 2 Severely Abnl Patterns

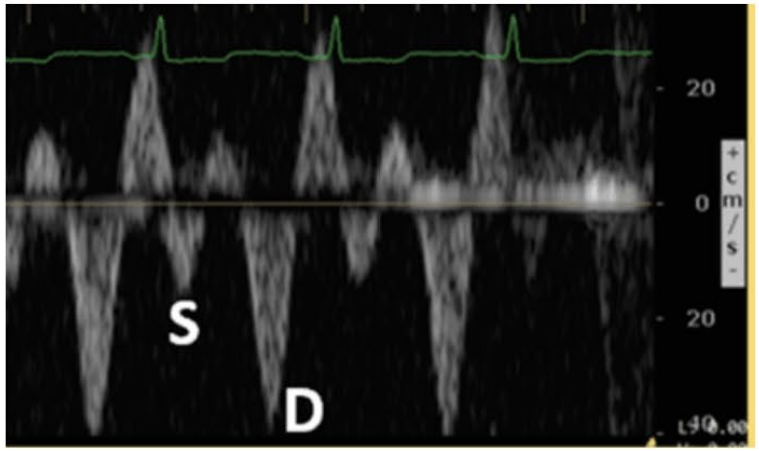
Normal Hepatic Vein Doppler: S>D



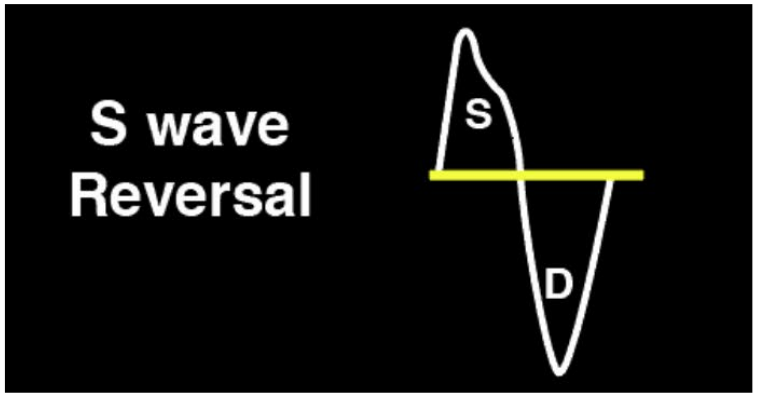


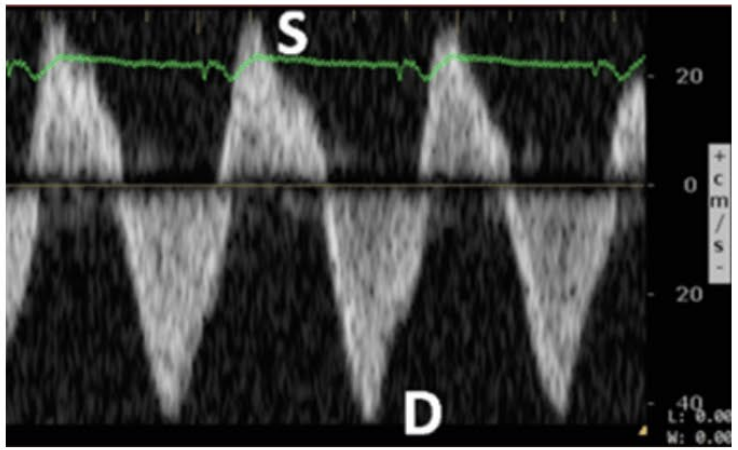
Mild Hepatic Vein Abnormality: S<D



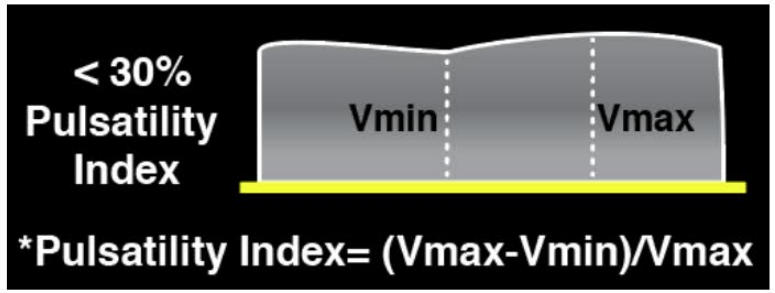


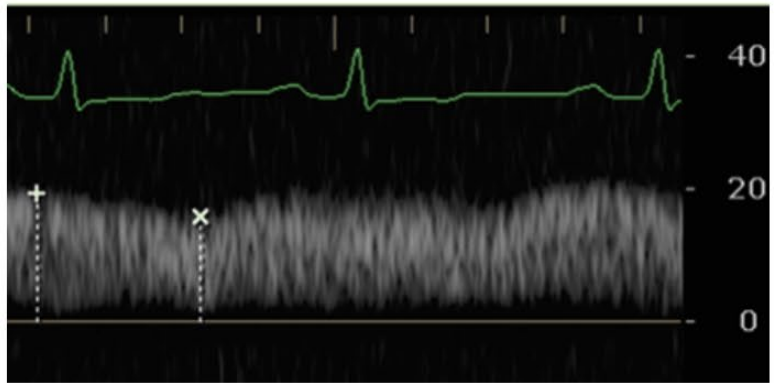
Severe Hepatic Vein Abnormality: S Reversal





Normal Portal Vein Doppler





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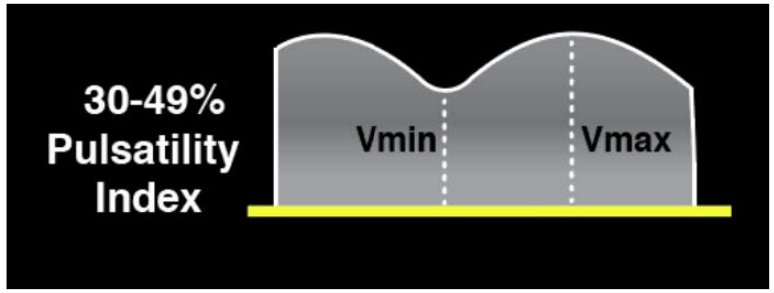
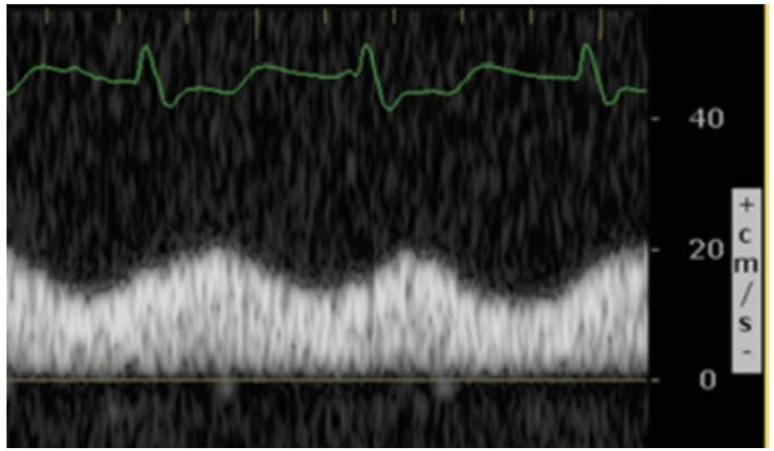
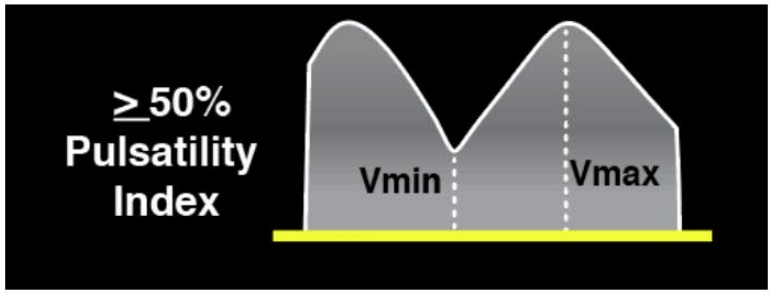
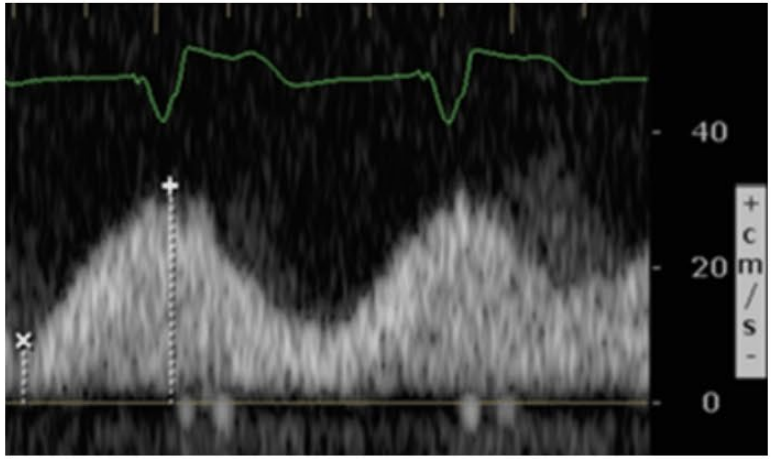


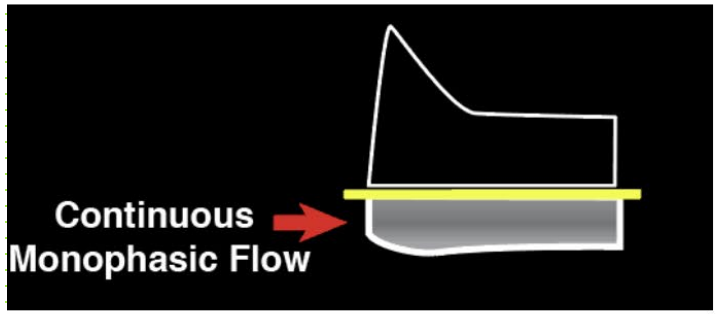


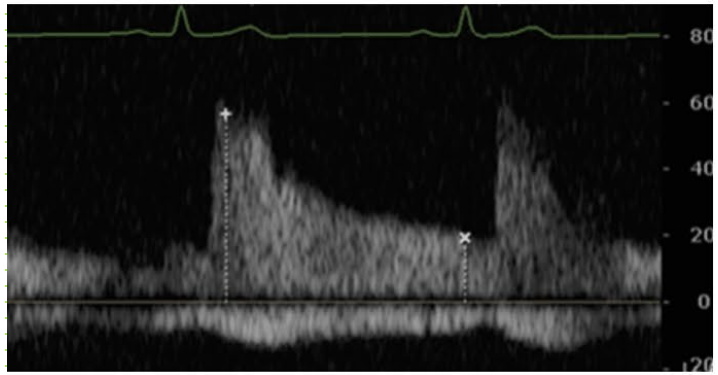
Severe Portal Vein Abnormality



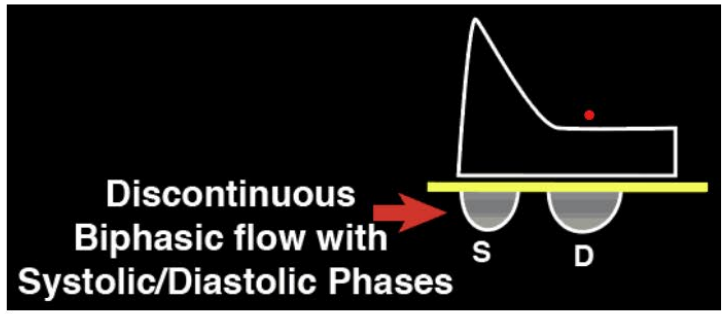


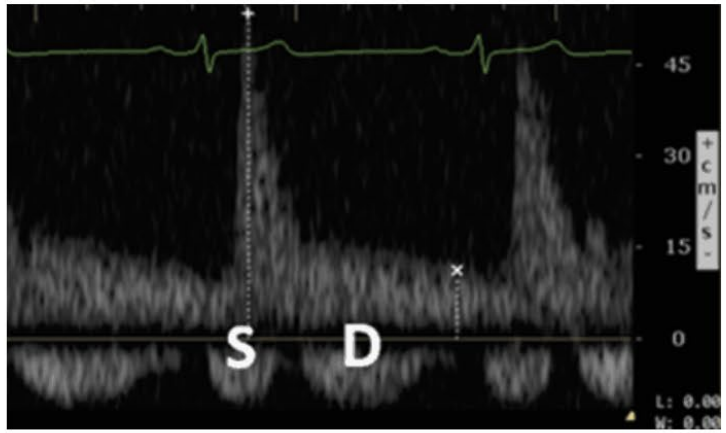
Normal Intrarenal Vein Doppler



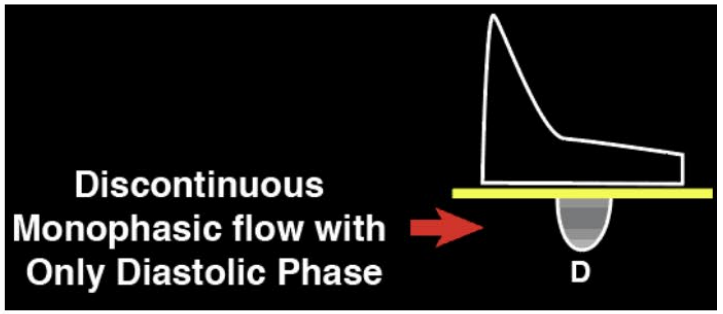


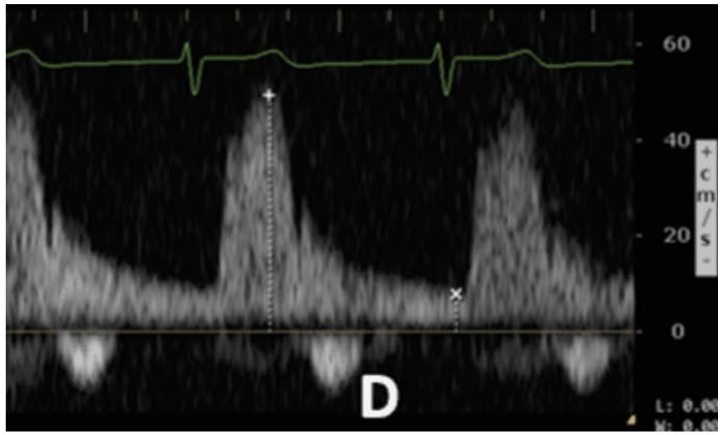
Mild Intrarenal Vein Abnormality



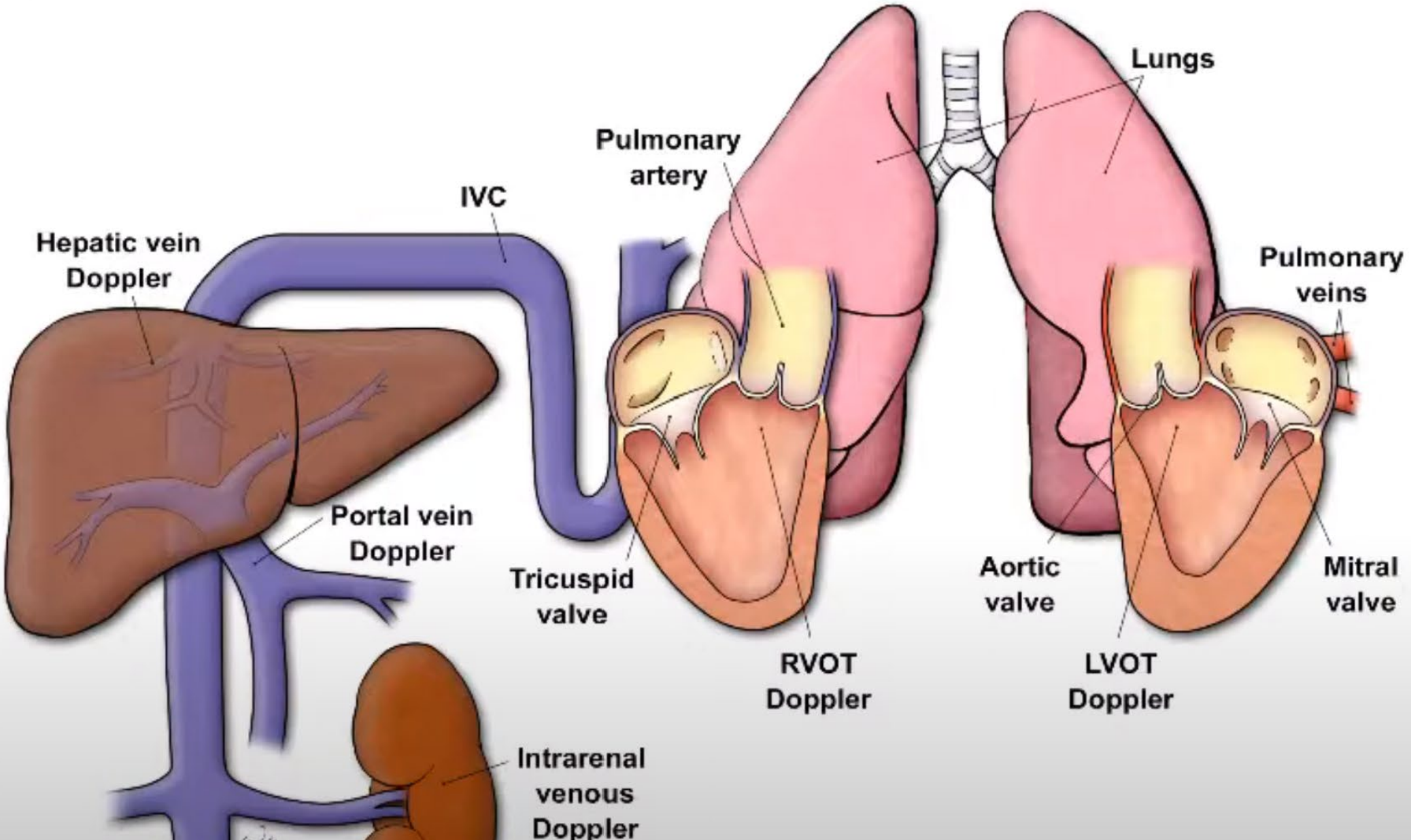


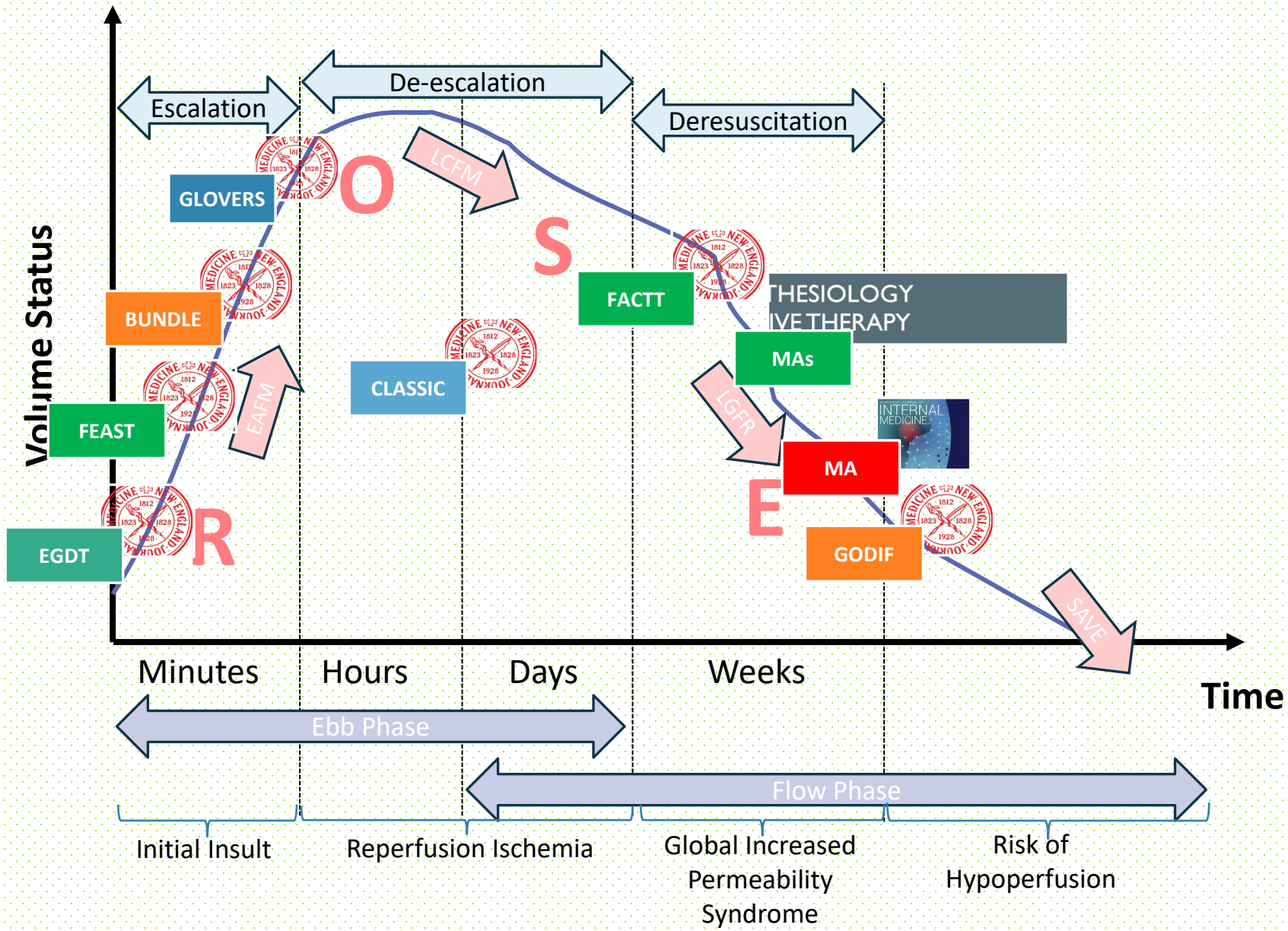
Severe Intrarenal Vein Abnormality





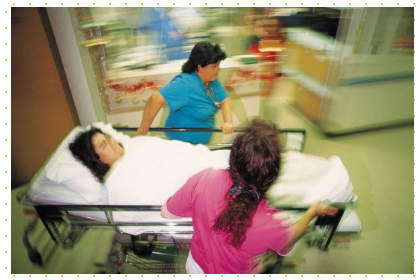
Congestion Cascade

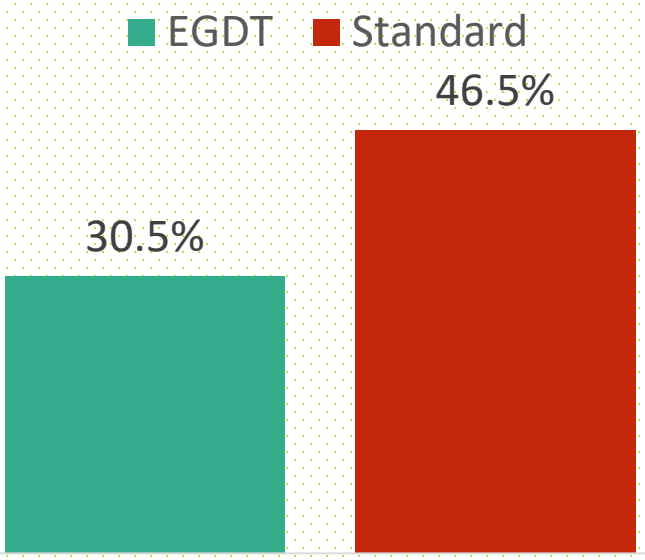




EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

EGDT Results





16% Absolute Risk Reduction
NNT 7

LOS 4 less days
$13-16,000 savings

Emanuel Rivers et al. N Engl J Med, 2001;345:1368-77

Early, Goal-Directed Therapy for Septic Shock - Patient-Level Meta-Analysis

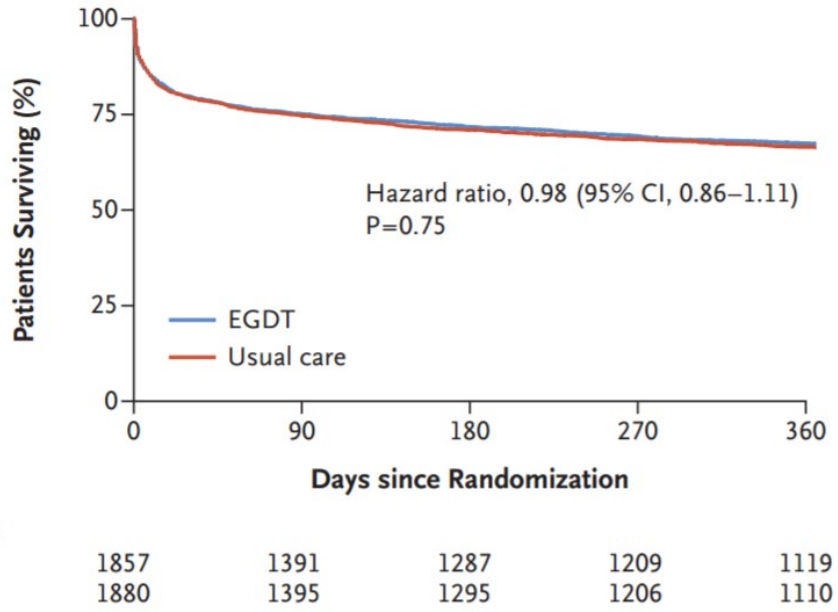


Figure 1. Patient Survival over a Period of 1 Year.

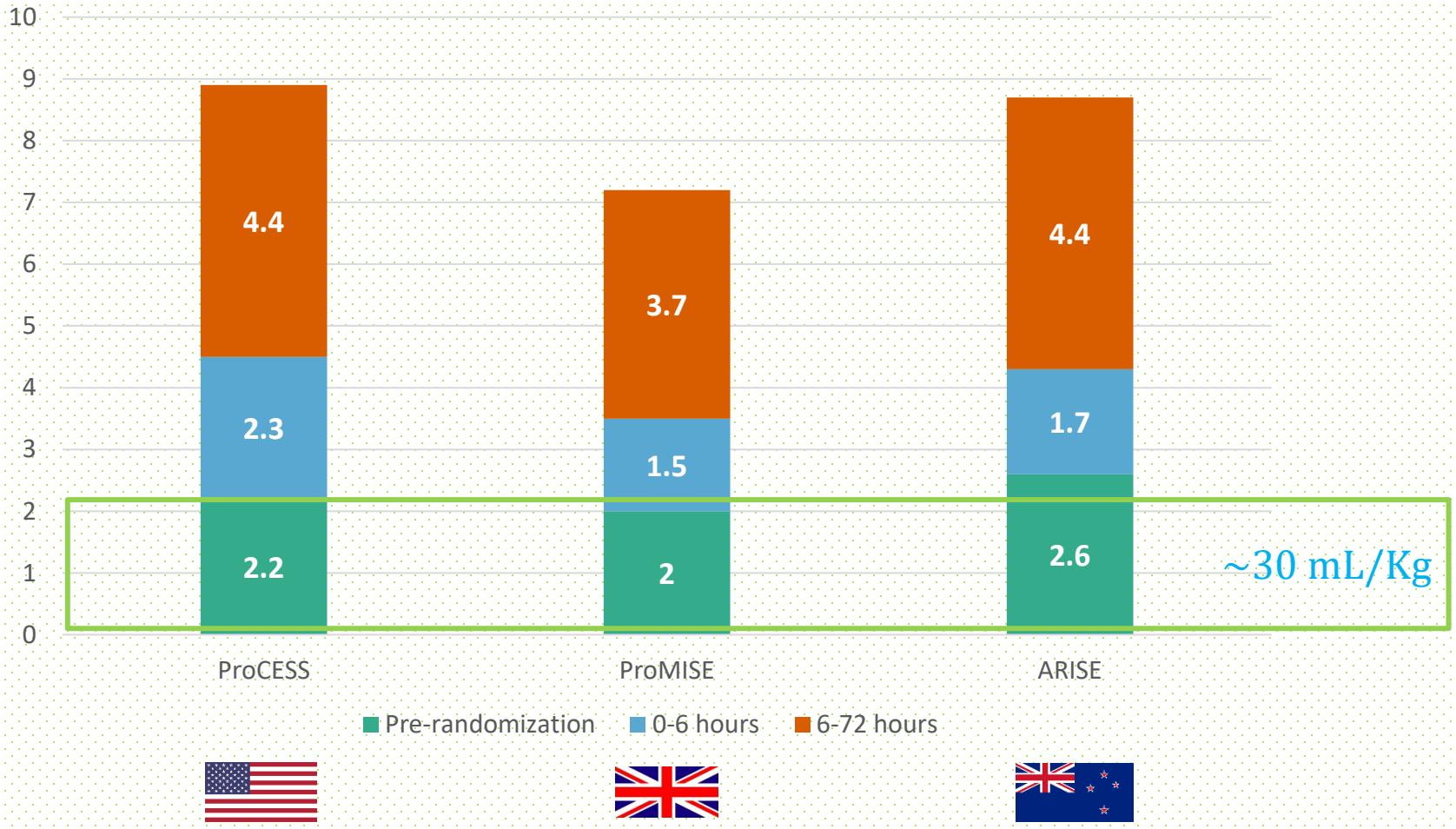
There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

ProCESS
ProMISE
ARISE

The PRISM Investigators ,NEJM, N Engl J Med 2017; DOI: 10.1056/NEJMoa1701380

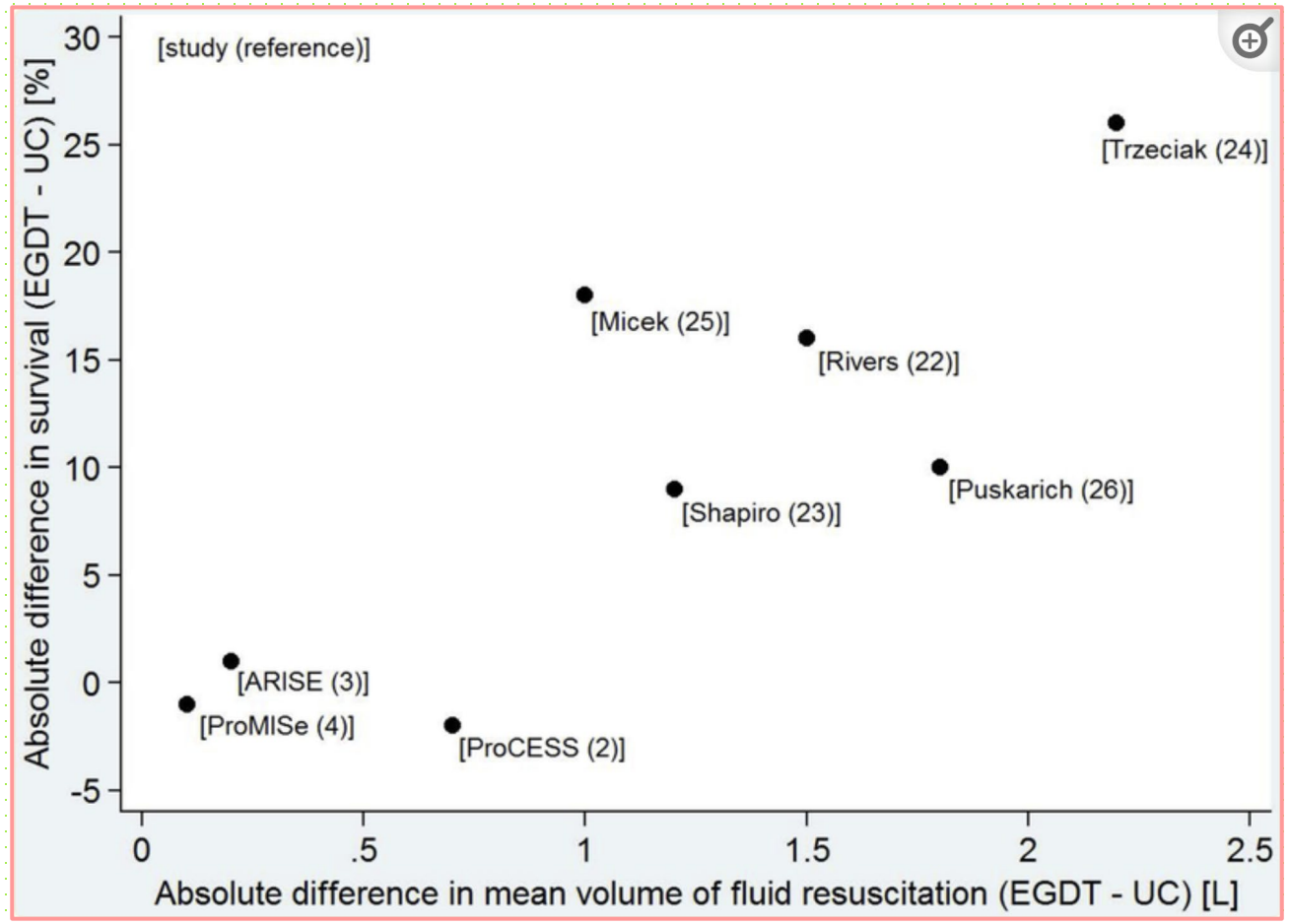
The NEW ENGLAND JOURNAL of MEDICINE

EGDT Trials: EGDT Evolved into Usual

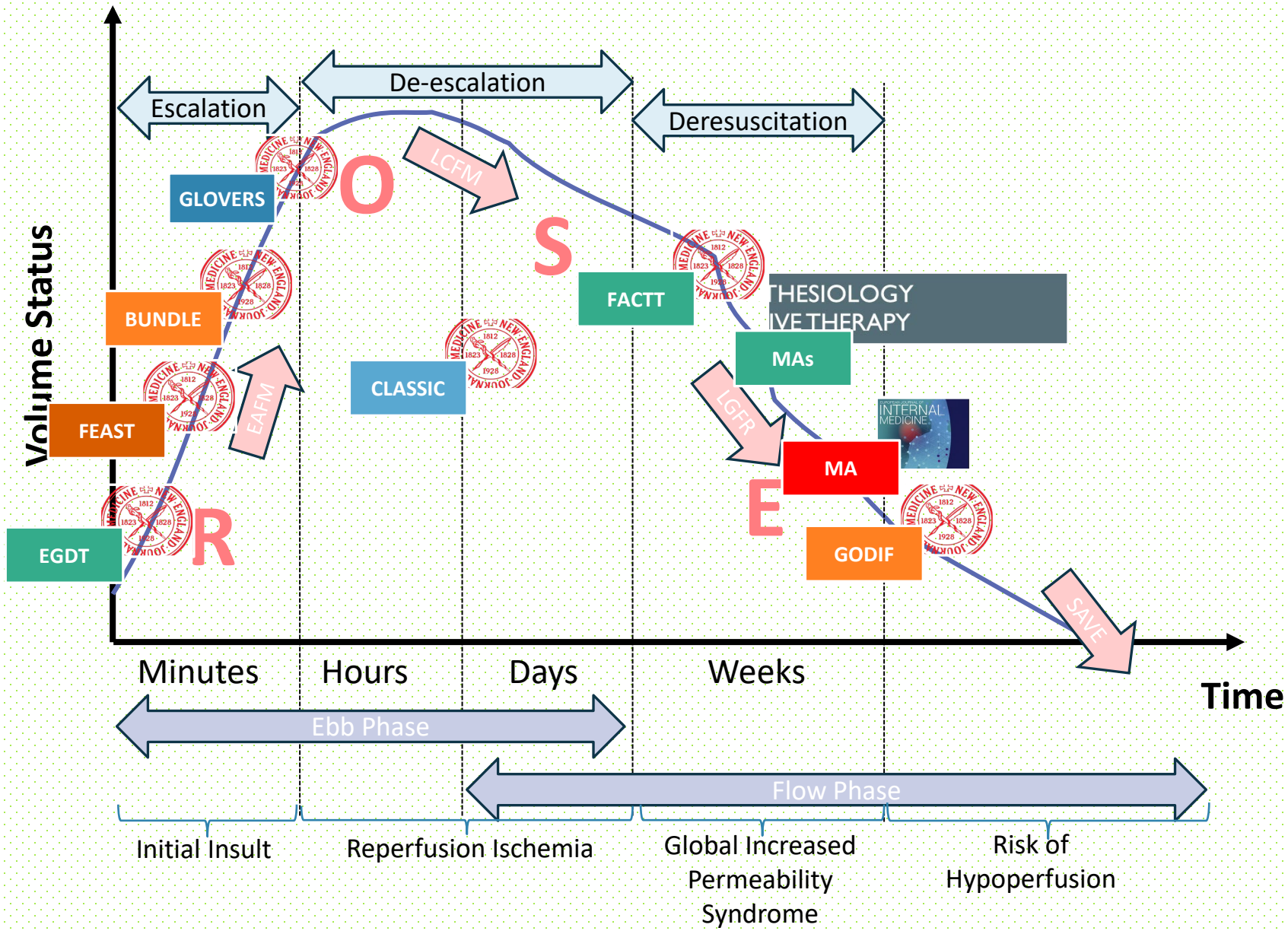


The PRISM Investigators ,NEJM, N Engl J Med 2017; DOI: 10.1056/NEJMoa1701380

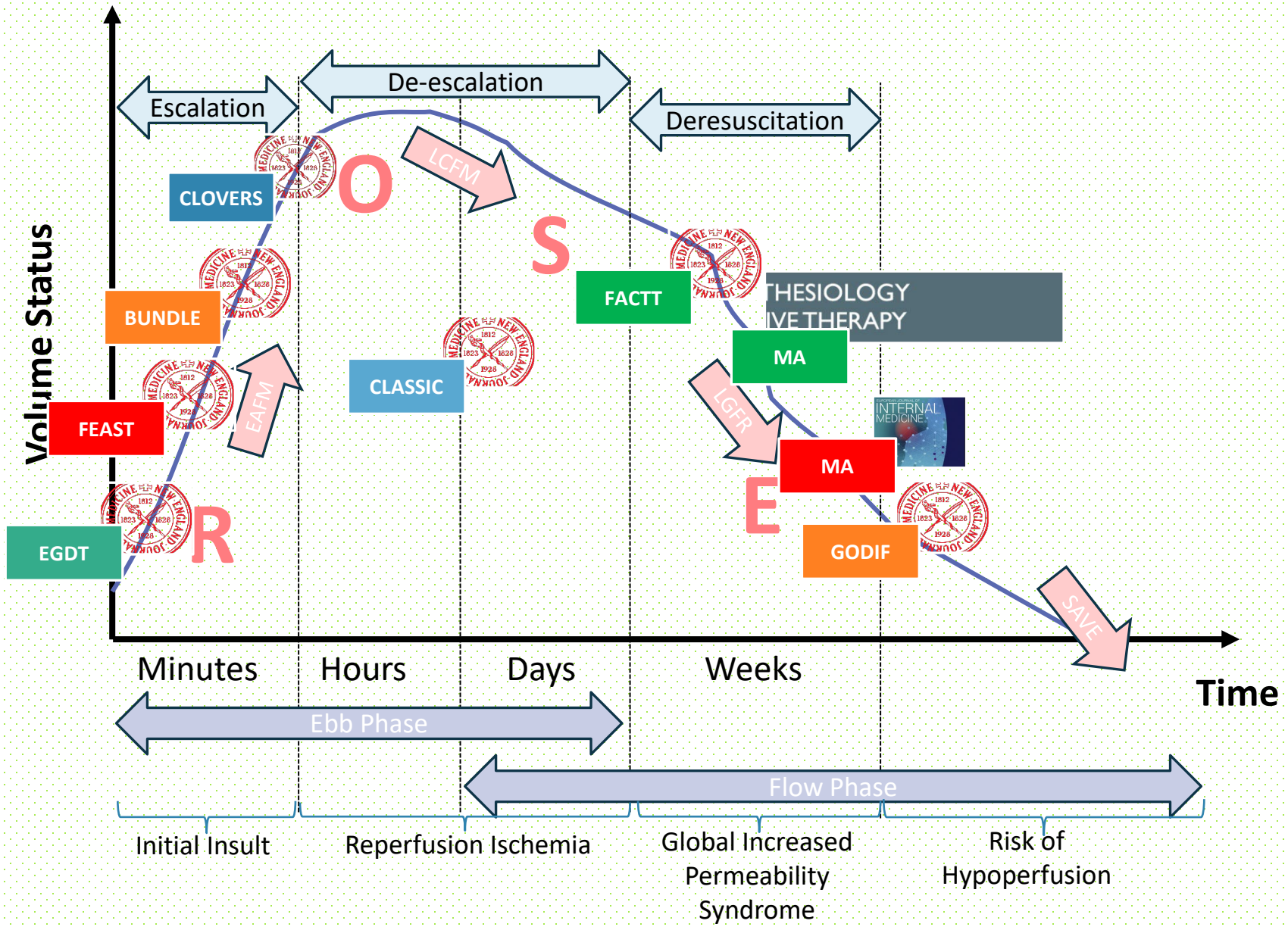
Mortality in Relation to Difference in Volume Resuscitation



Self WH, et al.; CLOVERS Protocol Committee and NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network Investigators. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med. 2018 Oct;72(4):457-466.



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal



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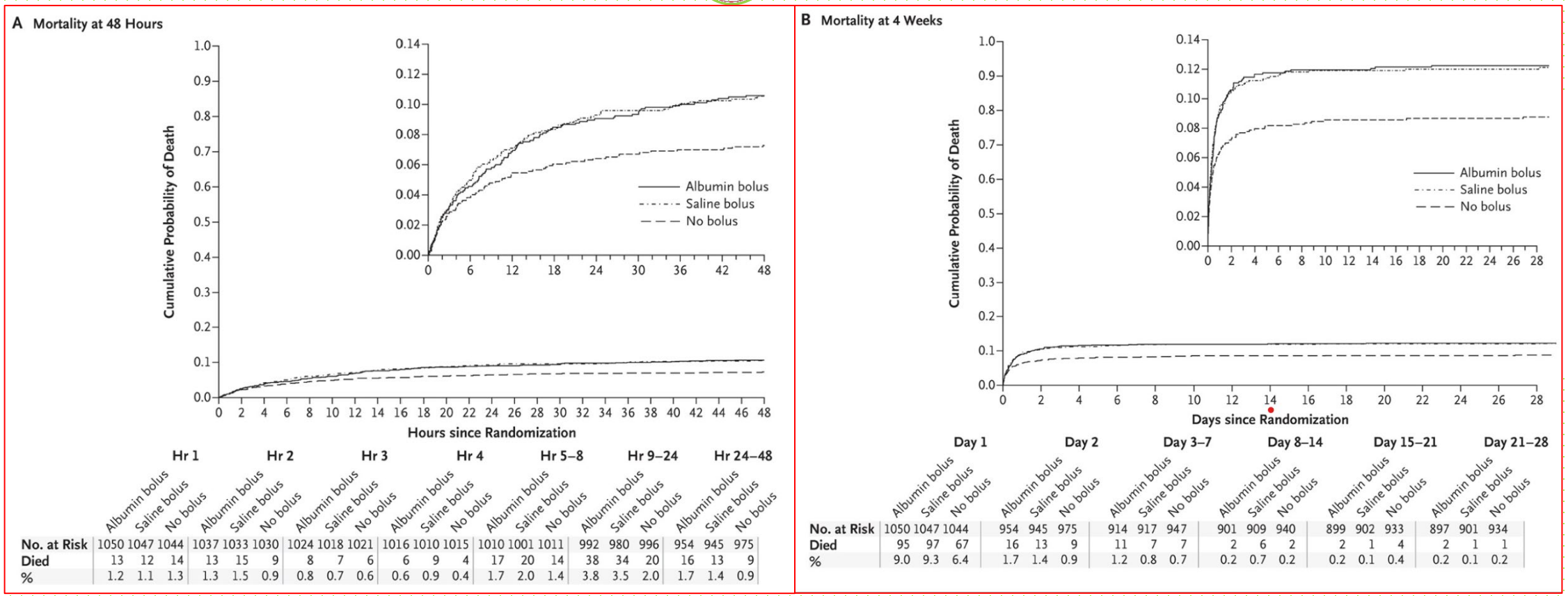
The Fluid Expansion as Supportive Therapy

FEAST

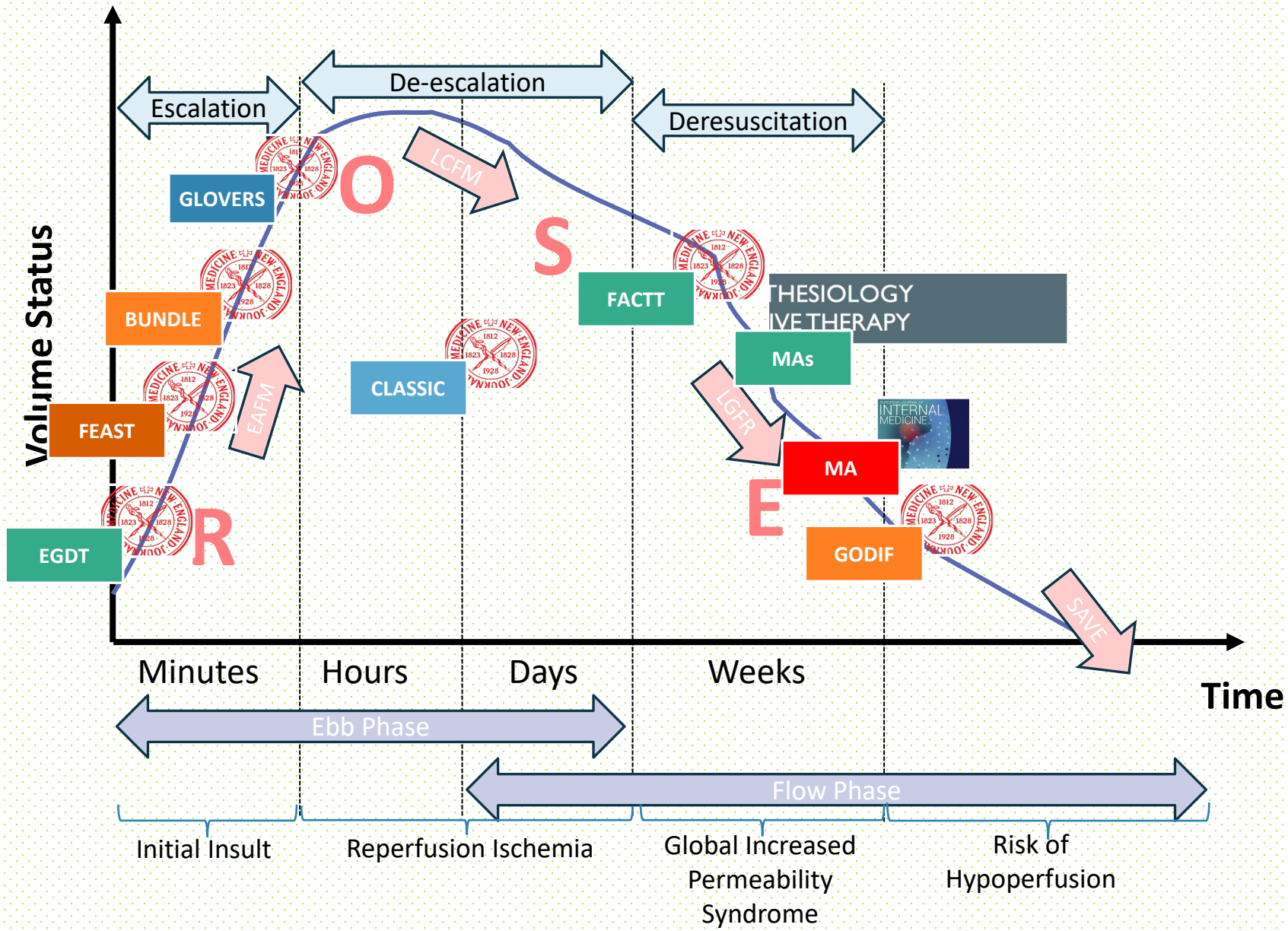


	Hr 1			Hr 2			Hr 3			Hr 4			Hr 5–8			Hr 9–24			Hr 24–48		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	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

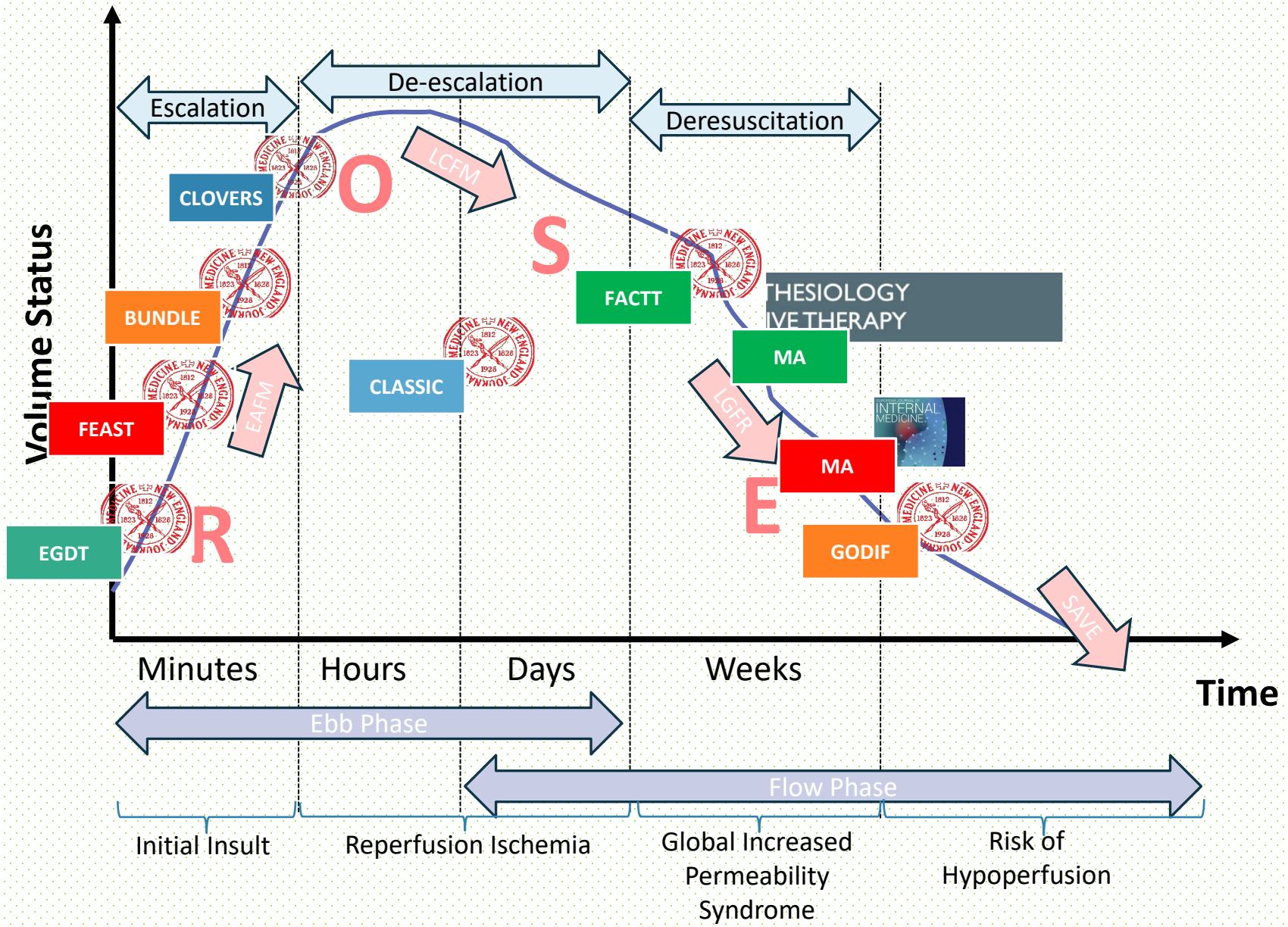
	Day 1			Day 2			Day 3–7			Day 8–14			Day 15–21			Day 21–28		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	954	945	975	914	917	947	901	909	940	899	902	933	897	901	934
Died	95	97	67	16	13	9	11	7	7	2	6	2	2	1	4	2	1	1
%	9.0	9.3	6.4	1.7	1.4	0.9	1.2	0.8	0.7	0.2	0.7	0.2	0.2	0.1	0.4	0.2	0.1	0.2

Over the course of 8 hours, the median cumulative volume of fluid received was 40.0 ml/kg in the albumin-bolus group, 40.0 ml/kg in the saline-bolus group, and 10.1 ml/kg in the control group

Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95.



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal



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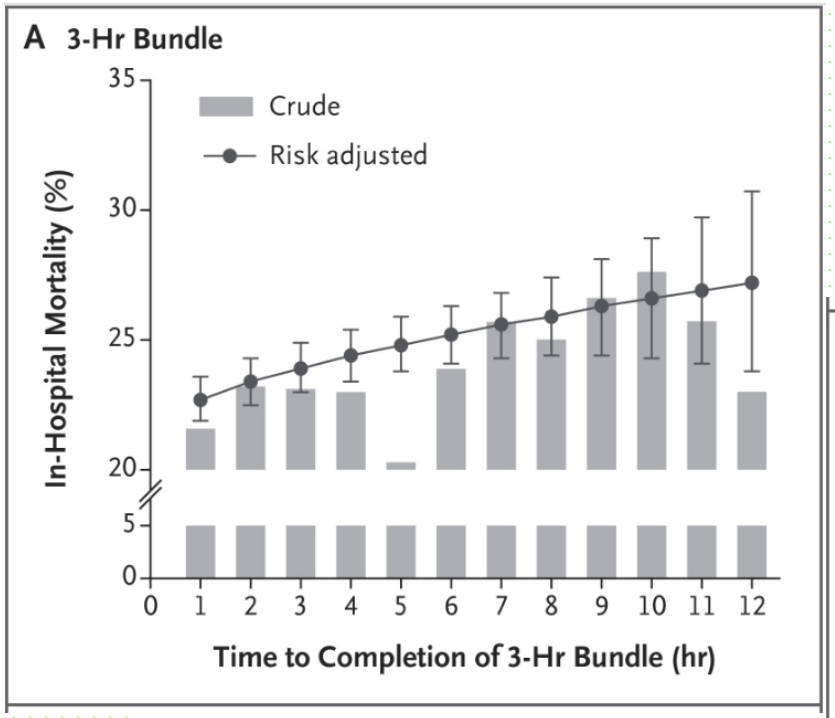
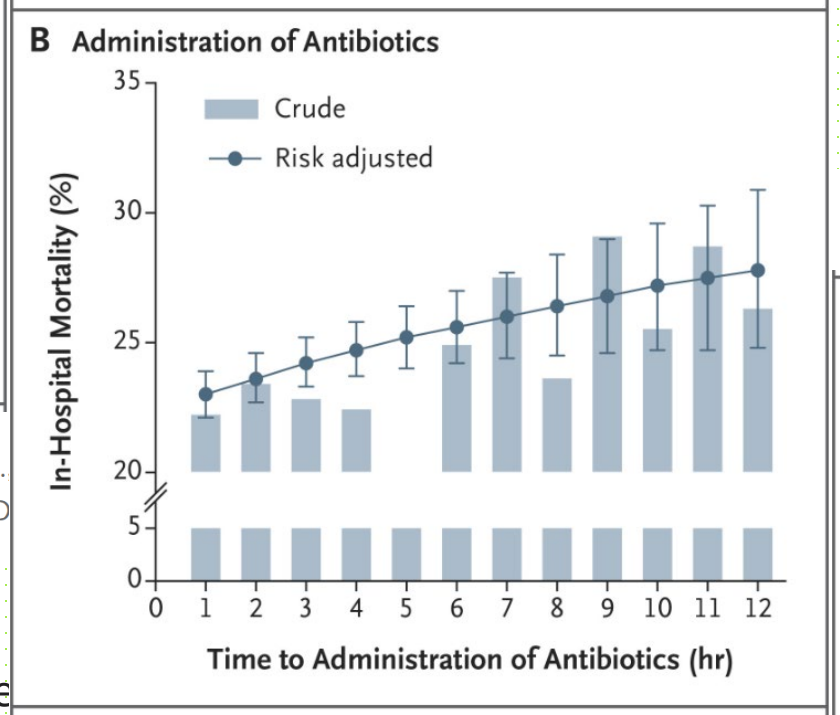
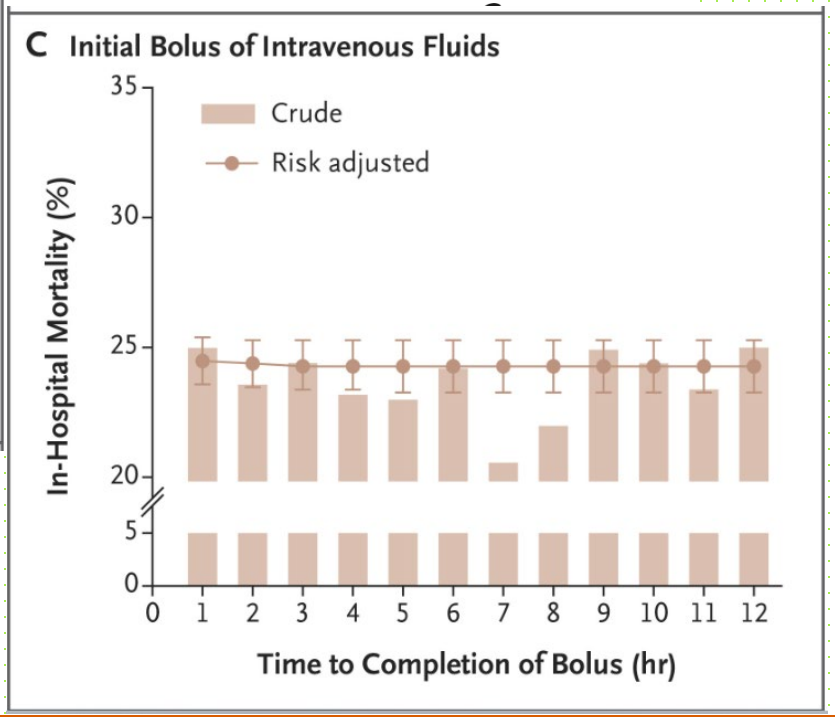
3-Hr Bundle: Blood cultures, broad-spectrum antibiotic agents, and lactate measurement



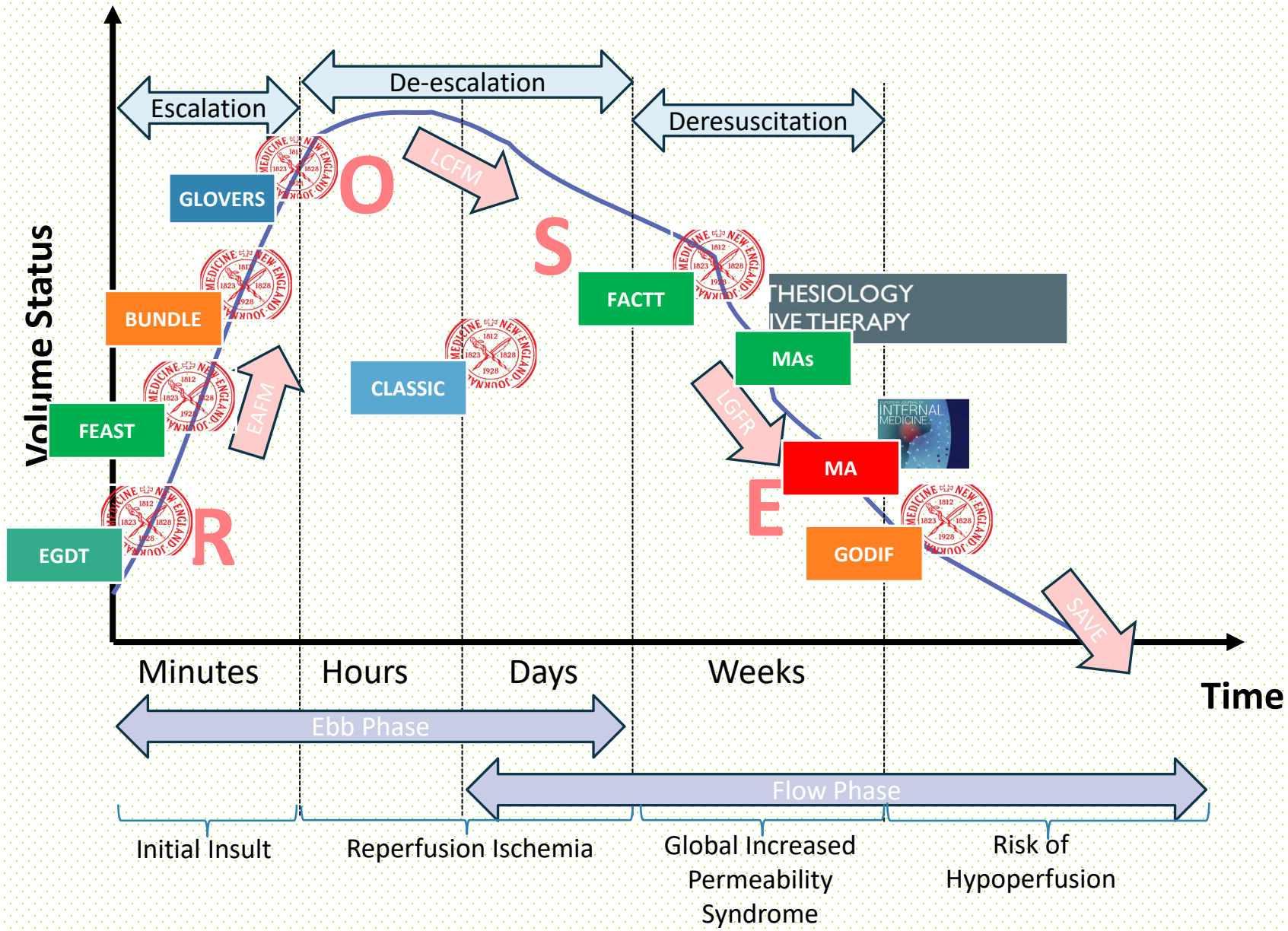
Christopher W. Seymour, M.D., Foster Gesten, M.D.
Lemeshow, Ph.D

NY State De





Time completion of initial fluid bolus was not associated with lower mortality (odds ratio, 1.01 per hour [95% CI, 0.99-1.02]; *P* = .21)



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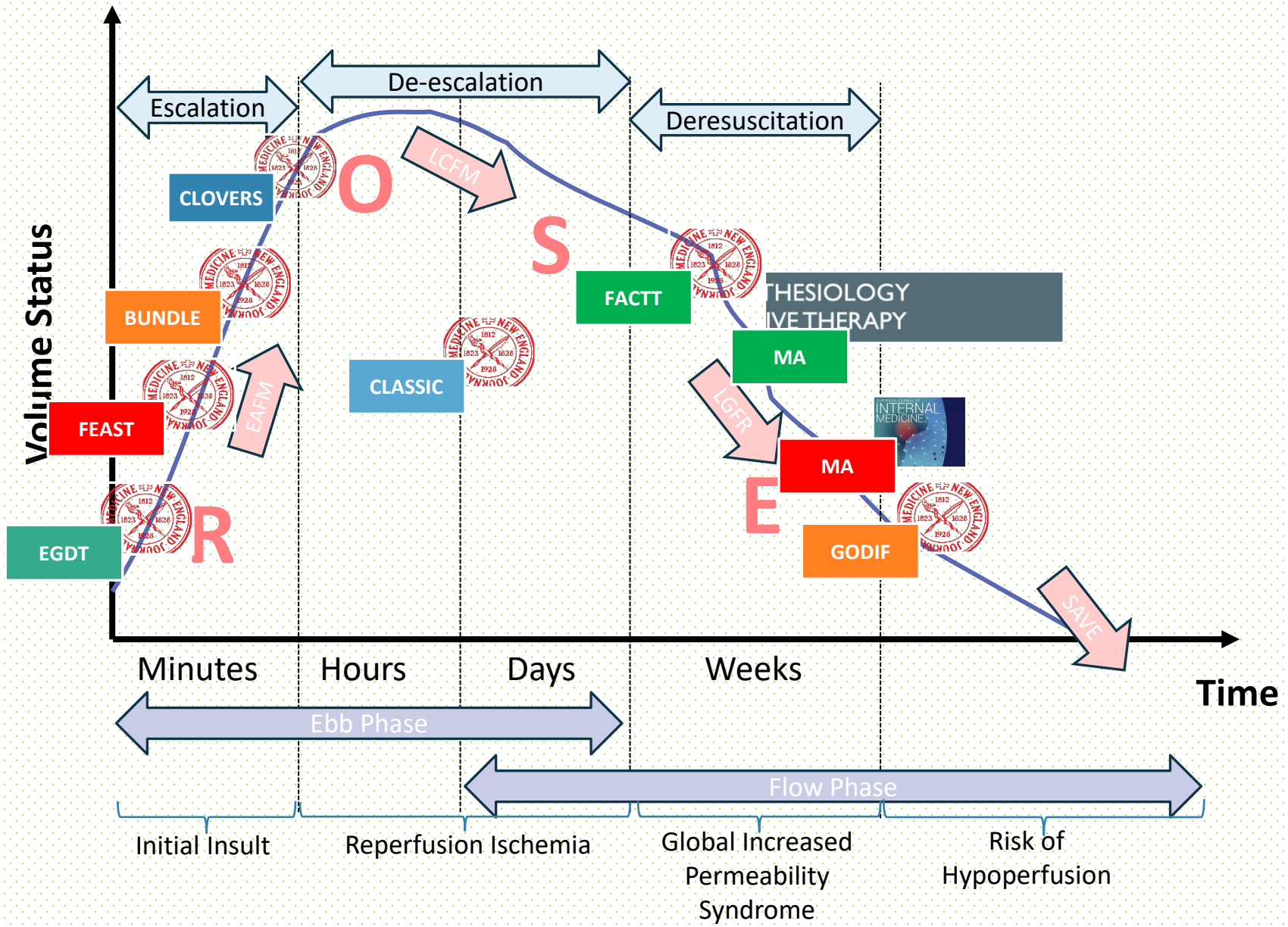


EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

icu REACH

January 21, 2023

Sepsis-induced hypotensive patients after 1-3 liters of fluid resuscitation

60 Centers

THE CLOVERS TRIAL

Does restrictive fluid strategy used during the first 24 hours of resuscitation lead to lower 90-day mortality compared to liberal fluid strategy?

MULTICENTER - UNBLINDED - RANDOMIZED

1563 Patients

Vasopressor-predominant Approach

Restrictive Strategy

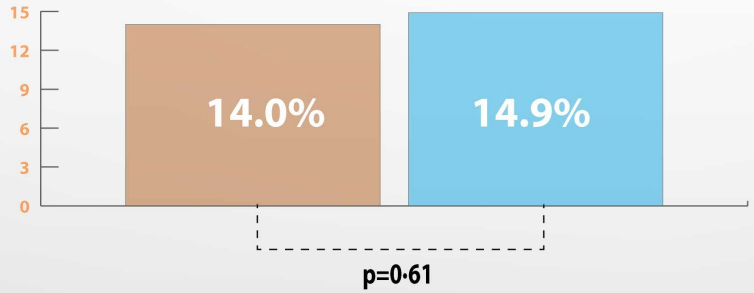
Vasopressors was used as the primary treatment for sepsis-induced hypotension with no fluid maintenance or boluses except rescue fluids for prespecified indications.

Median fluid over 6-hours (IQR): 500 (130-1097) mL.
Medan fluid over 24-hours (IQR): 1267 (555-2279) mL.
Vasopressor administration during first 24 hours: 59.0%.

Time to first vasopressor (hr): 1.8±3.4.
Duration of vasopressor use during first 24-hr period (hr): 9.6±10.0.

782 PATIENTS

90-day Mortality



Fluid-predominant Approach

Liberal Strategy

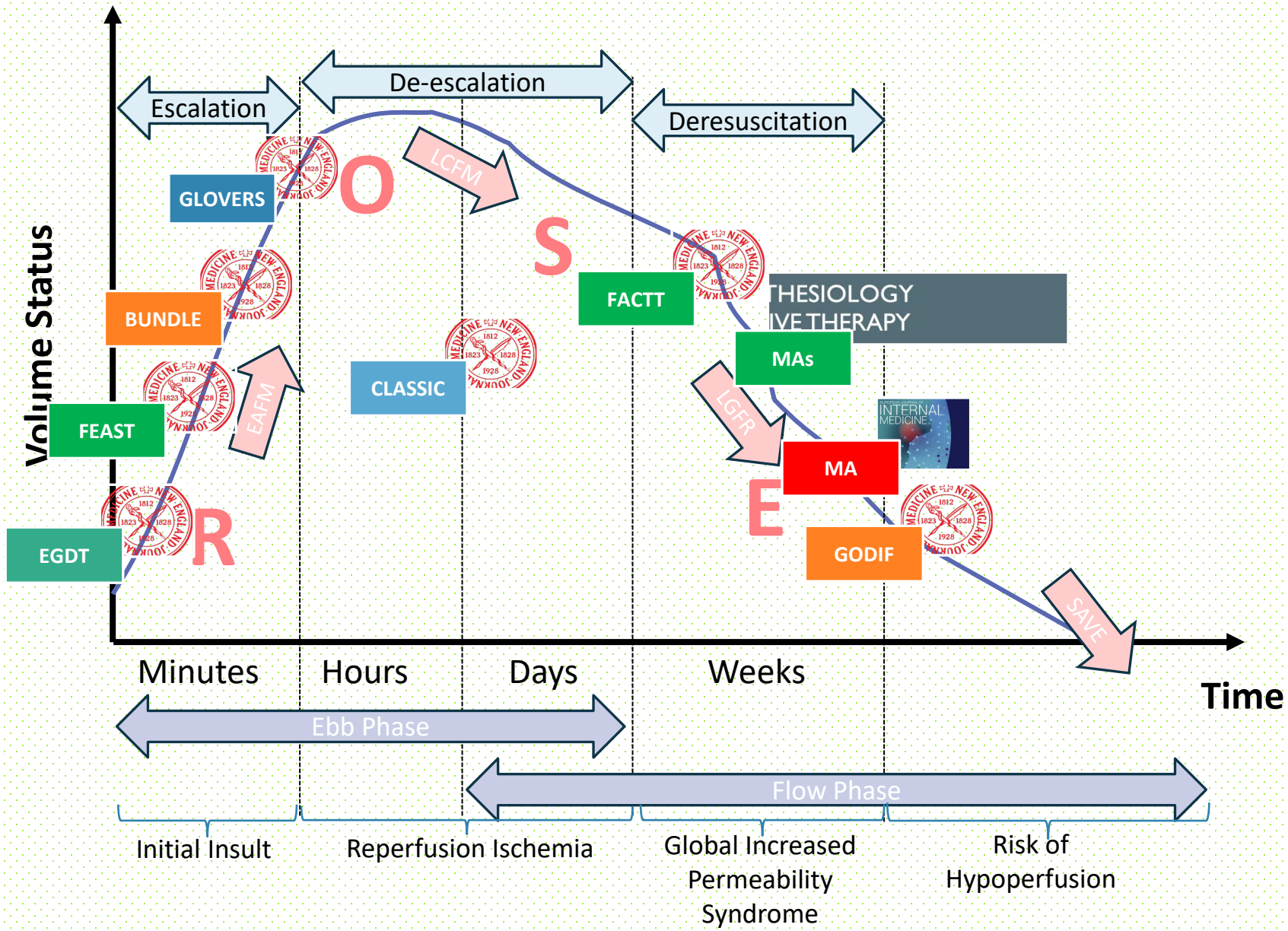
Recommended an initial 2000-ml intravenous infusion of isotonic crystalloid, followed by fluid boluses administered on the basis of clinical triggers (e.g., tachycardia) with “rescue vasopressors” permitted for prespecified indications.

Median fluid over 6-hours (IQR): 2300 (2000 to 3000) mL.
Medan fluid over 24-hours (IQR): 3400 (2500 to 4495) mL.
Vasopressor administration during first 24 hours: 37.2%.
Time to first vasopressor (hr): 3.2±4.7.
Duration of vasopressor use during first 24-hr period (hr): 5.4±8.6.

781 PATIENTS

Compared to a liberal fluid strategy, earlier vasopressor use in a restrictive fluid strategy did not result in any significant difference in mortality rate prior to discharge by day 90.

DOI: 10.1056/NEJMoa2212663



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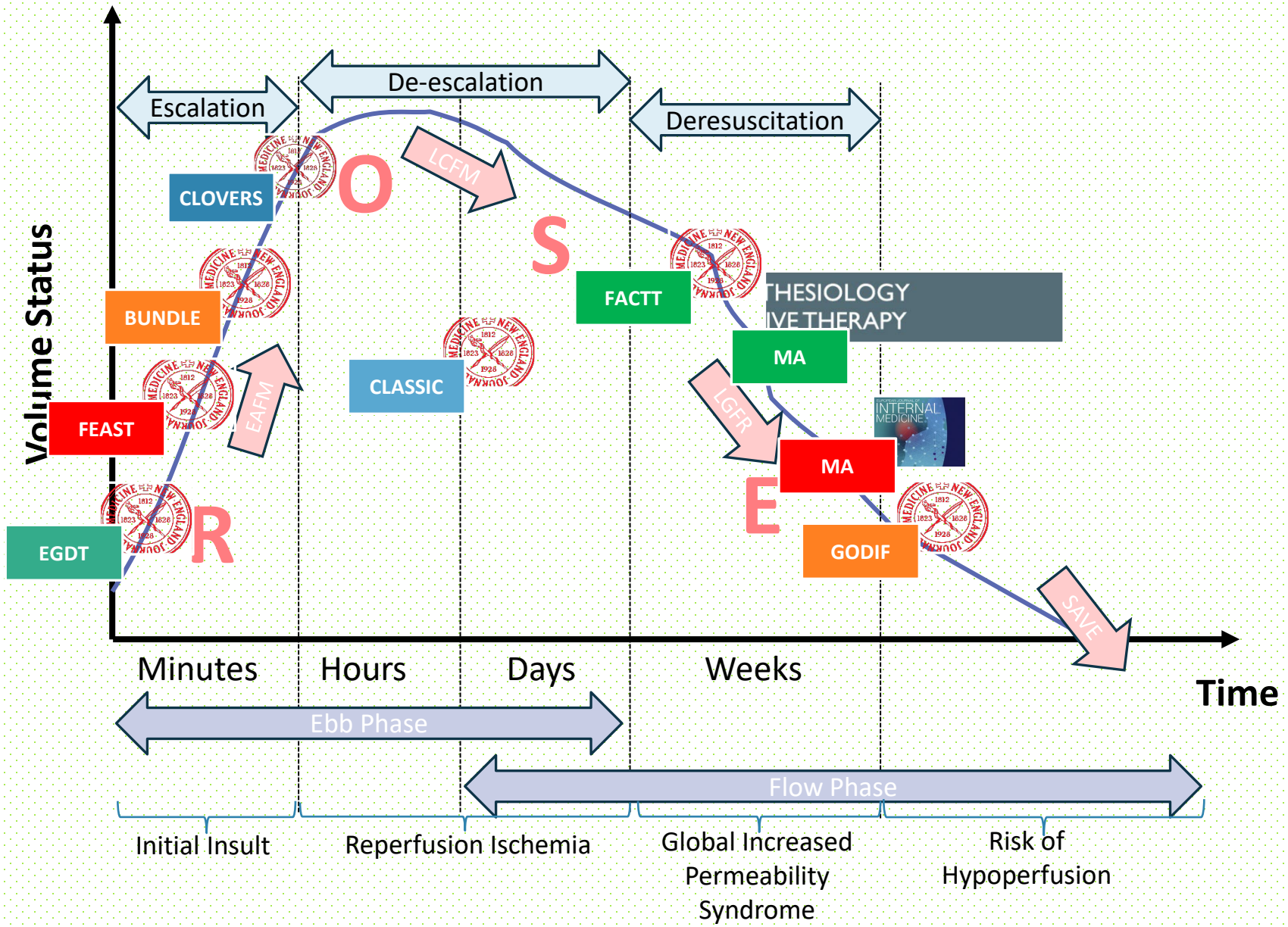

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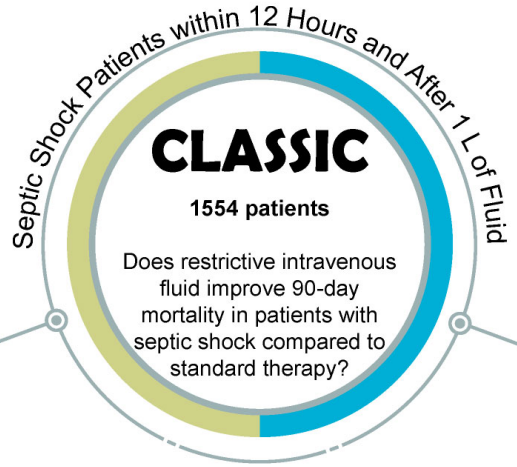
Restriction of Intravenous Fluid in ICU Patients with Septic Shock

June 17, 2022



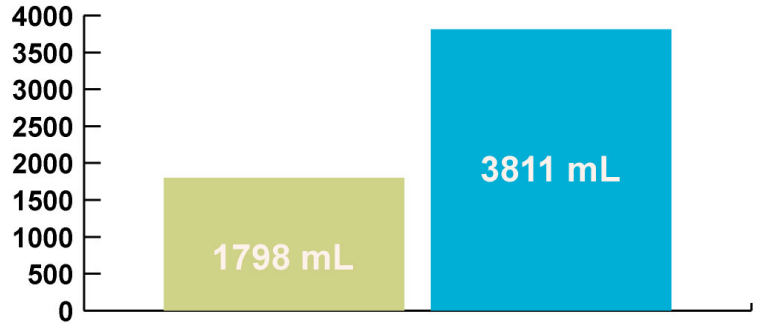
770 patients

Fluids were given for hypoperfusion state, fluid losses, dehydration, or daily intake of 1 L.

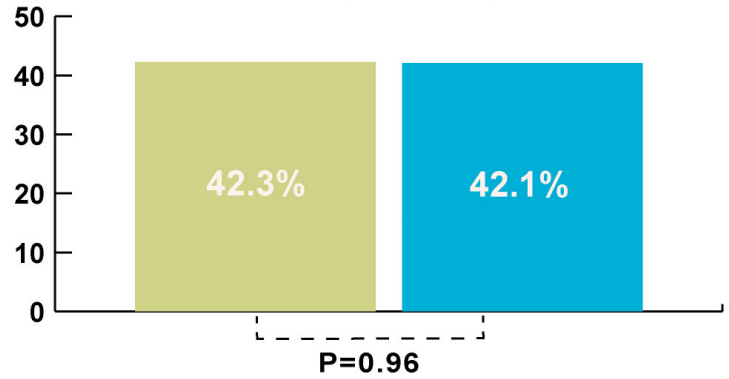
784 patients

Fluids were given as per surviving sepsis campaign, for observed losses or dehydration, or for maintenance as per local ICU protocols.

Median Fluid Volume in ICU



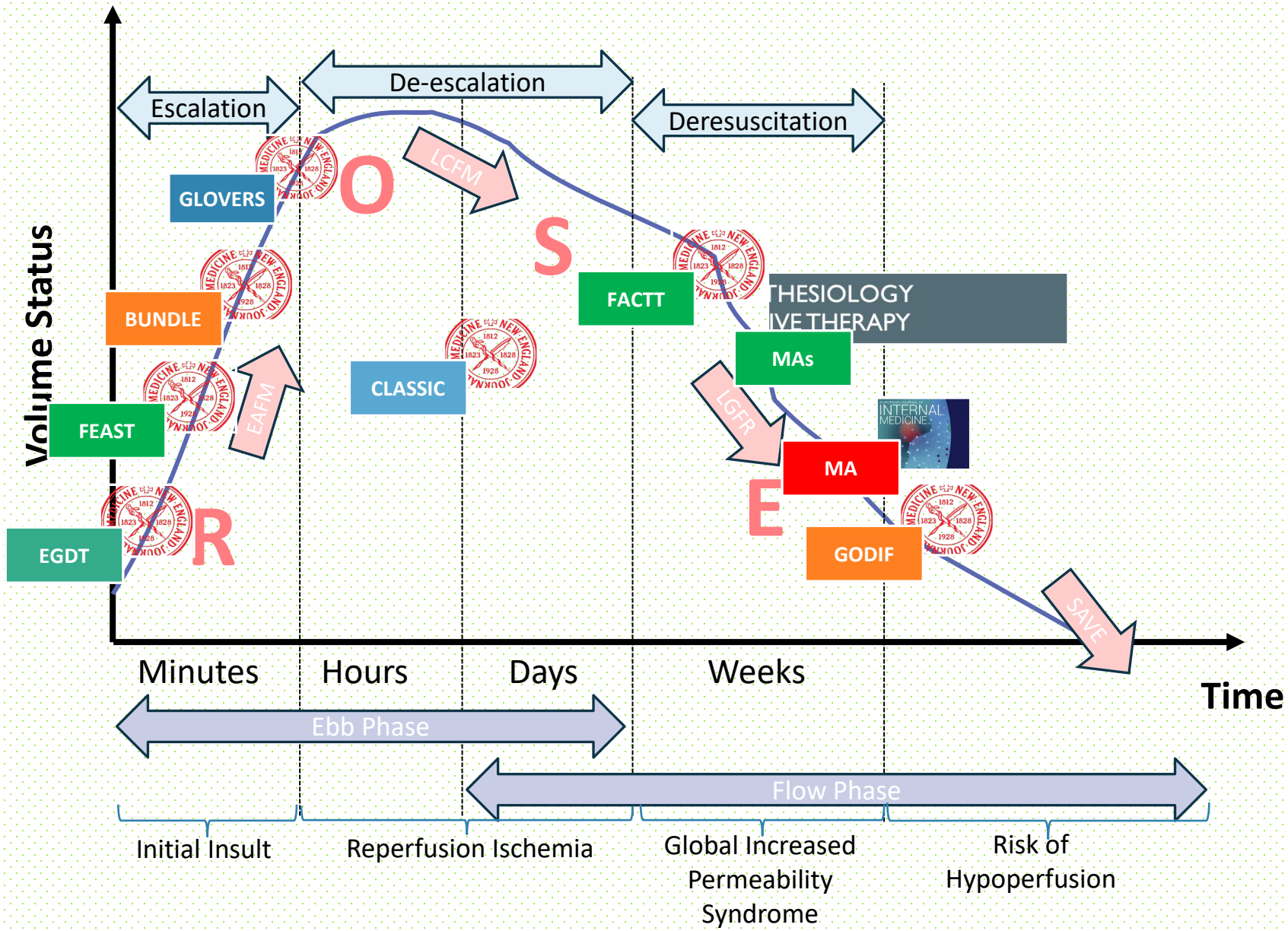
90-day Mortality



Absolute difference, 0.1; 95% CI, −4.7 to 4.9

CONCLUSION

Restrictive fluid strategy did not reduce 90-day mortality in patients with septic shock compared to standard intravenous fluid therapy.



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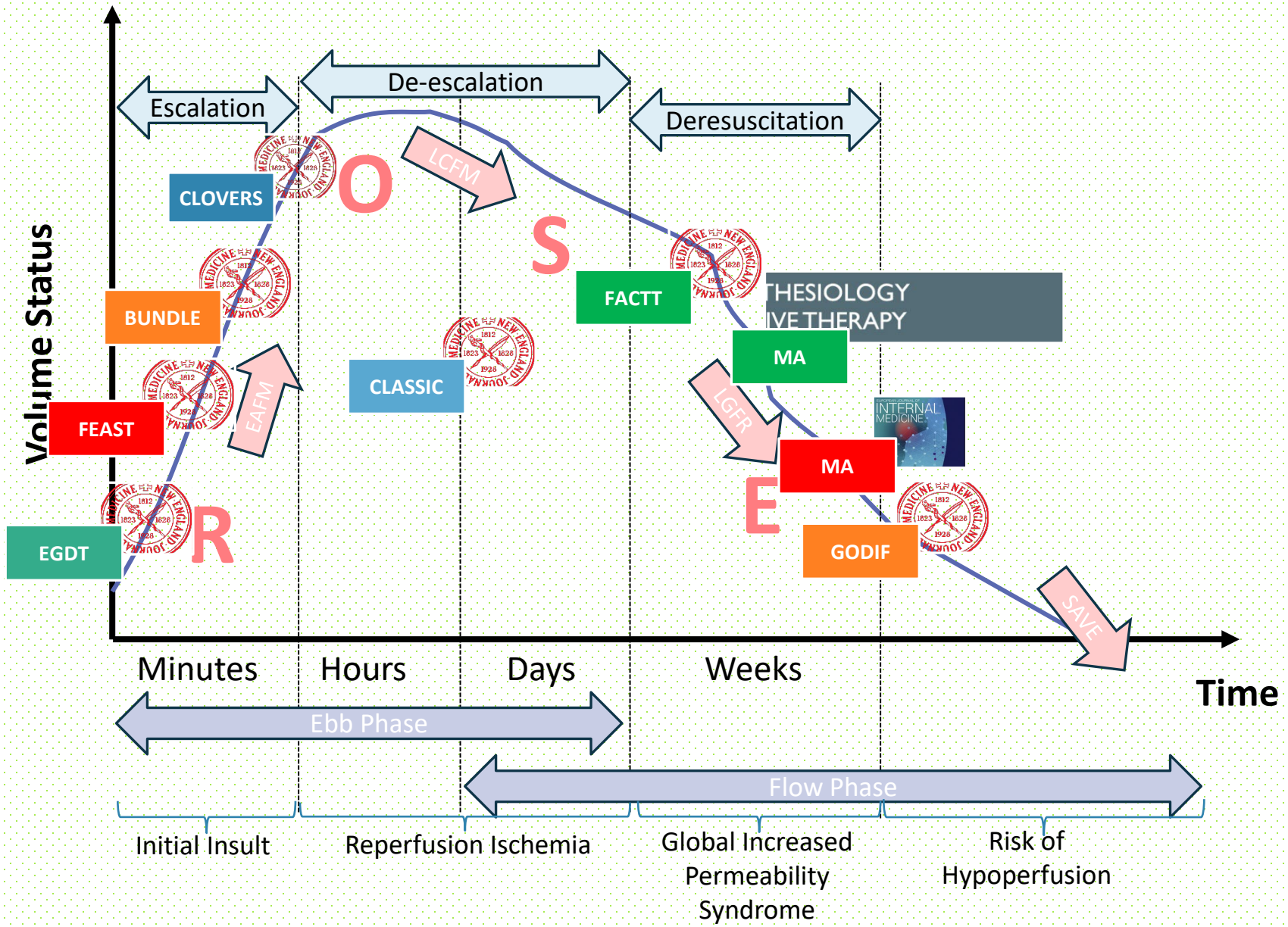

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Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The FACTT Randomized Clinical Trial

June 15, 2006

Adults with early ALI/ARDS within 48 hours

1000 Patients

Is conservative fluid strategy associated with improved mortality compared to liberal fluid strategy?

503

CONSERVATIVE

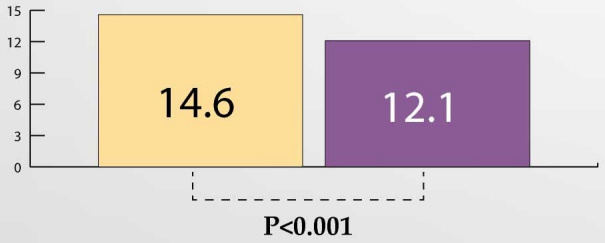
7-day fluid balance was -136 mL

497

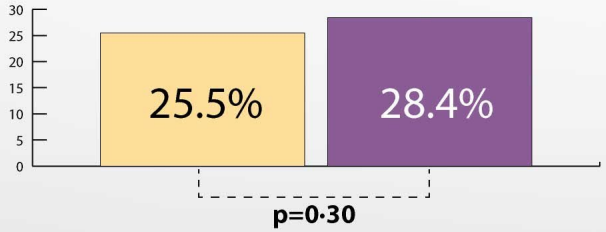
LIBERAL

7-day fluid balance was +6992 mL

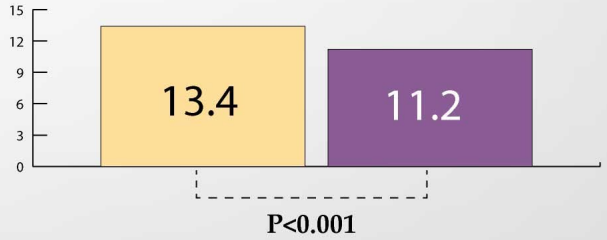
Number of Ventilator-free Days



60-day Mortality

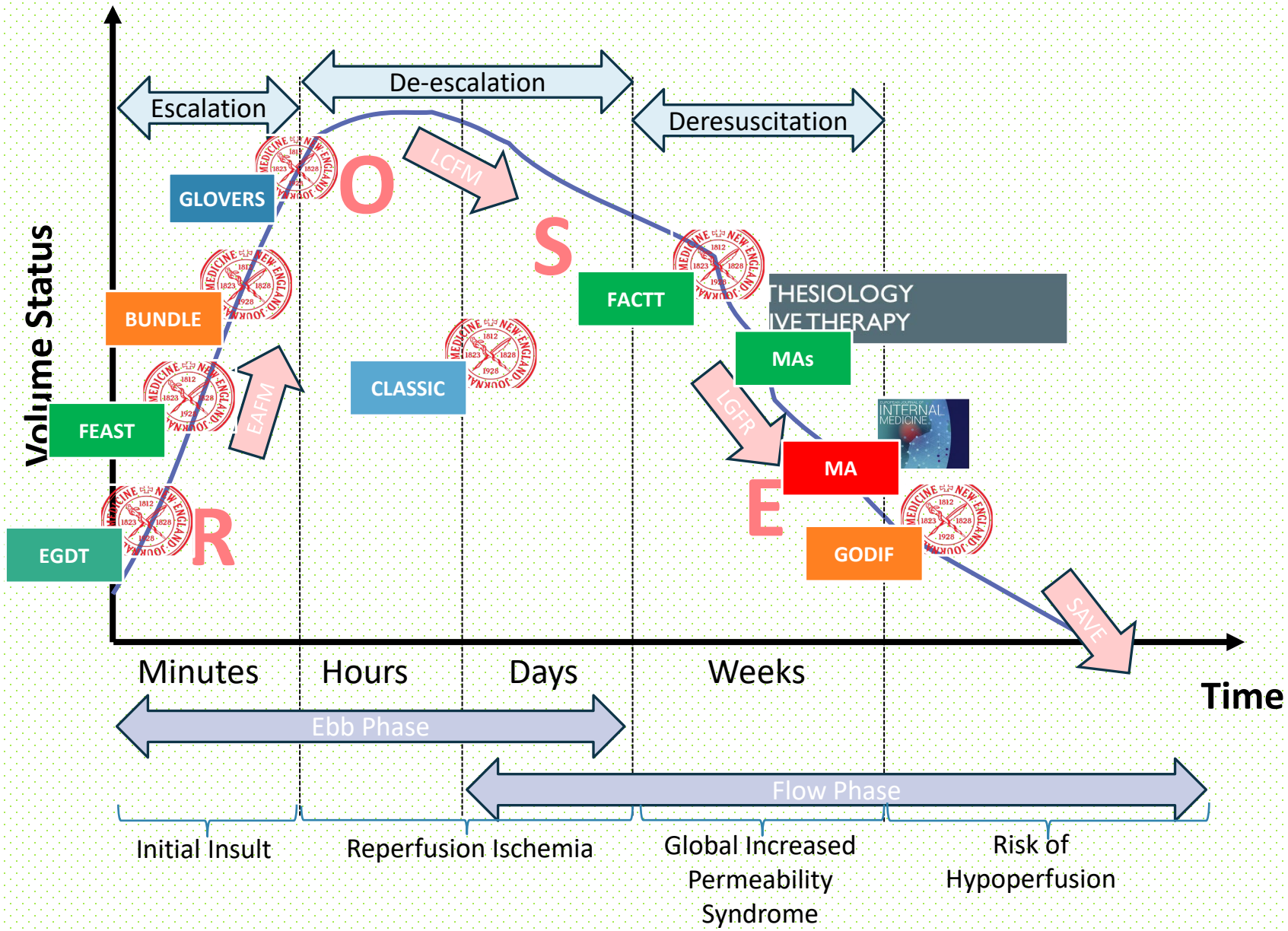


Nymber of Days Not Spent in the ICU



Conservative fluid strategy did not improve 60-day mortality but improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures.

N Engl J Med 2006; 354:2564-2575



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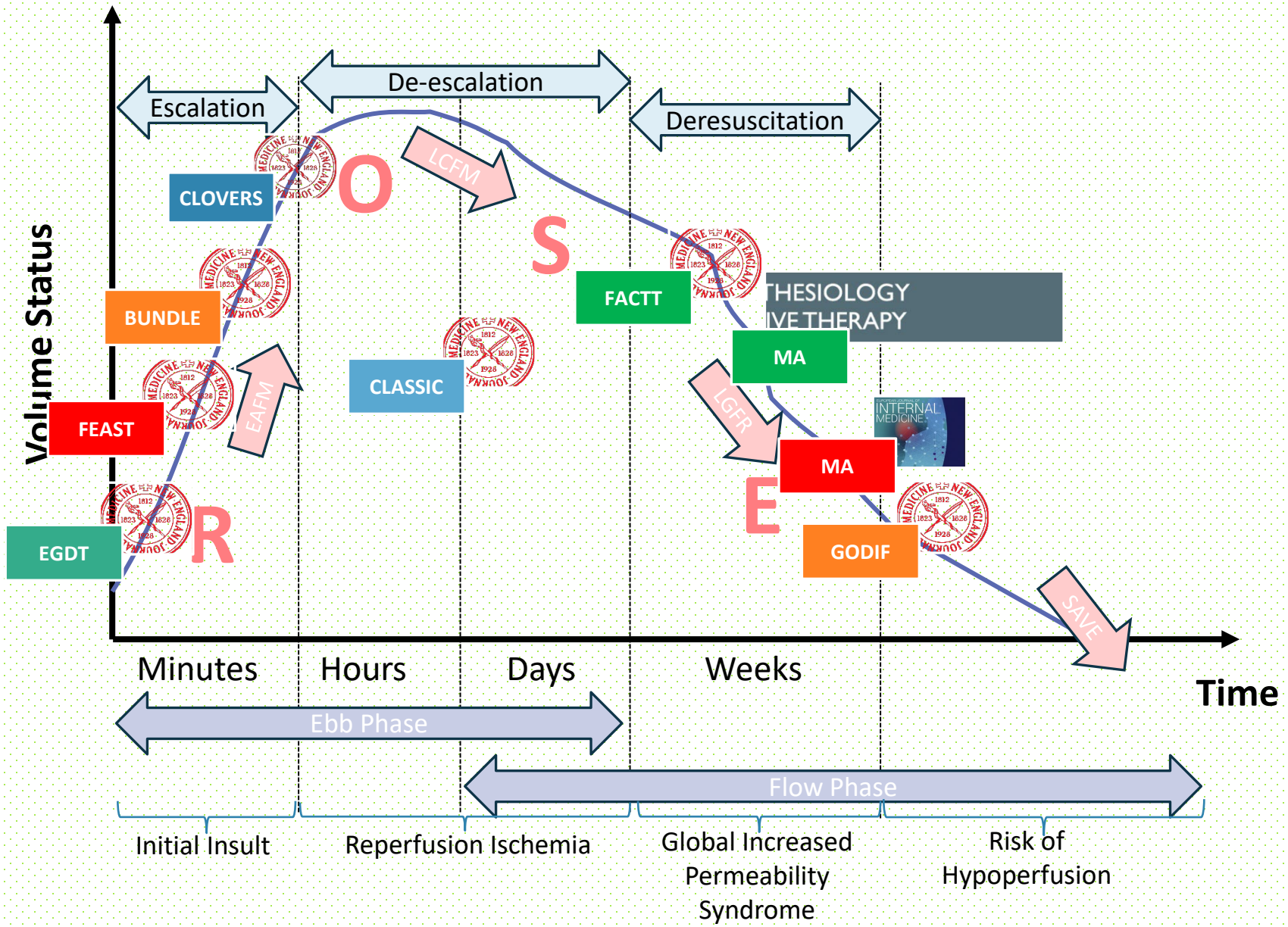

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VIA MEDICA

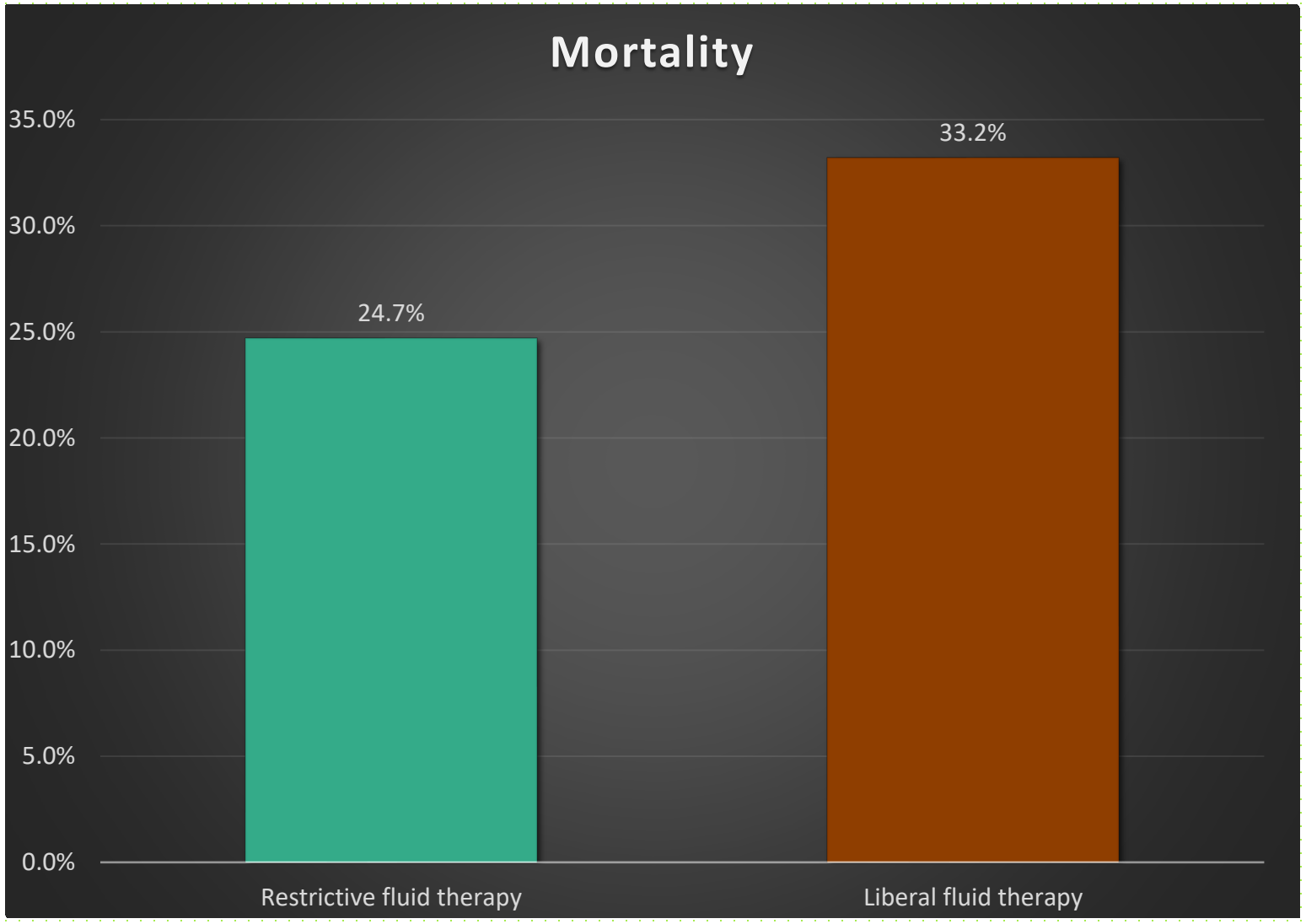
REVIEWS

Anaesthesiology Intensive Therapy
2014, vol. 46, no 5, 361–380
ISSN 1642–5758
DOI: 10.5603/AIT.2014.0060
www.ait.viamedica.pl

Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice

Manu L.N.G. Malbrain[1], Paul E. Marik[2], Ine Witters[1], Colin Cordemans[1], Andrew W. Kirkpatrick[3], Derek J. Roberts[3, 4], Niels Van Regenmortel[1]

19,902 critically ill patients were studied from one individual patient meta-analysis, 11 randomised controlled clinical trials, seven interventional studies, 24 observational studies, and four case series met the inclusion criteria

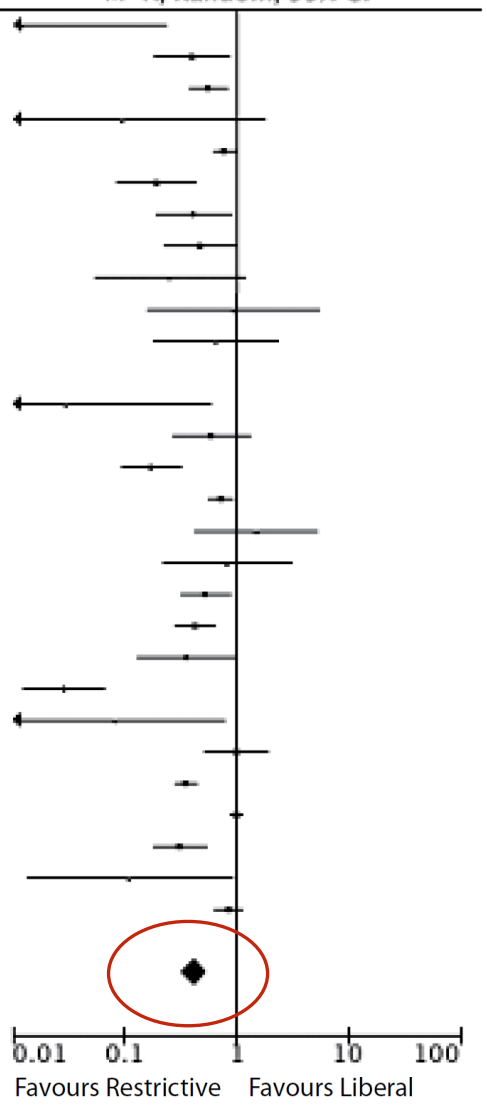


Malbrain ML, et al. Anaesthesiol Intensive Ther. 2014 Nov-Dec;46(5):361-80

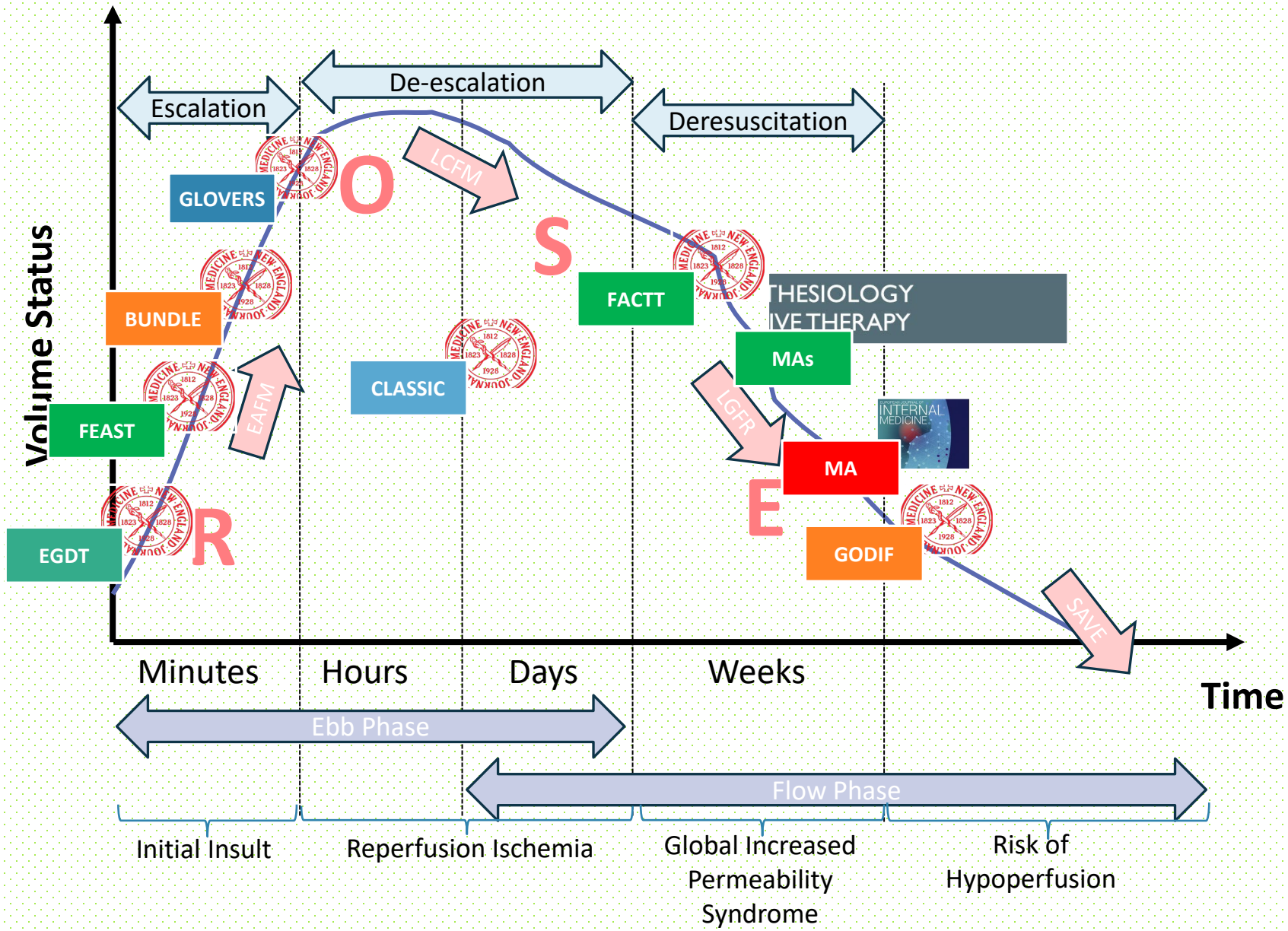
Study or Subgroup	Restrictive FM Events	Total	Liberal FM Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alsous 2000	0	11	20	25	0.7%	0.01 [0.00, 0.23]
Balogh 2003	11	71	27	85	3.9%	0.39 [0.18, 0.87]
Bouchard 2009	72	226	97	211	5.2%	0.55 [0.37, 0.81]
Brandstrup 2003	0	69	4	62	0.7%	0.09 [0.00, 1.77]
Caironi 2014 (SS)	243	558	281	563	5.6%	0.77 [0.61, 0.98]
Cordemans 2012 (CLI)	11	41	54	82	3.8%	0.19 [0.08, 0.44]
Cordemans 2012 (PAL)	16	57	28	57	4.0%	0.40 [0.19, 0.88]
Goldstein 2005	25	60	34	56	4.1%	0.46 [0.22, 0.97]
Lowell 1990	3	29	6	19	2.0%	0.25 [0.05, 1.16]
Martin 2002	3	19	3	18	1.7%	0.94 [0.16, 5.39]
Martin 2005	7	20	9	20	2.6%	0.66 [0.18, 2.35]
Mc Ardle 2009	0	9	0	11		Not estimable
Michael 2004	6	17	9	9	0.7%	0.03 [0.00, 0.60]
Mitchell 1992	18	52	23	49	3.9%	0.60 [0.27, 1.33]
Murphy 2009	30	124	57	88	4.6%	0.17 [0.10, 0.32]
Payen 2008	181	572	214	548	5.6%	0.72 [0.56, 0.92]
Pupelis 2012	8	75	4	55	2.6%	1.52 [0.43, 5.34]
Pupelis 2012 (IAH)	7	60	4	29	2.5%	0.83 [0.22, 3.08]
Rivers 2001	40	130	61	133	4.9%	0.52 [0.32, 0.87]
Rosenberg 2009	32	159	236	635	5.1%	0.43 [0.28, 0.65]
Schuller 1991	9	34	17	34	3.2%	0.36 [0.13, 0.99]
Shum 2011	91	599	43	50	3.8%	0.03 [0.01, 0.07]
Simmons 1987	10	18	15	16	1.2%	0.08 [0.01, 0.77]
Stewart 2009	23	122	23	122	4.4%	1.00 [0.53, 1.90]
The RENAL Study 2012	241	747	403	705	5.7%	0.36 [0.29, 0.44]
The SAFE Study 2004	726	3497	729	3500	5.8%	1.00 [0.89, 1.12]
Vaara 2012	65	207	45	76	4.8%	0.32 [0.18, 0.54]
Walsch 2008	1	49	9	57	1.3%	0.11 [0.01, 0.91]
Wiedemann 2006	128	503	141	497	5.5%	0.86 [0.65, 1.14]
Total (95% CI)		**8135**		**7812**	**100.0%**	**0.42 [0.32, 0.55]**
Total events	2007		2596			

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 210.79$, df = 27 ($P < 0.00001$); $I^2 = 87\%$

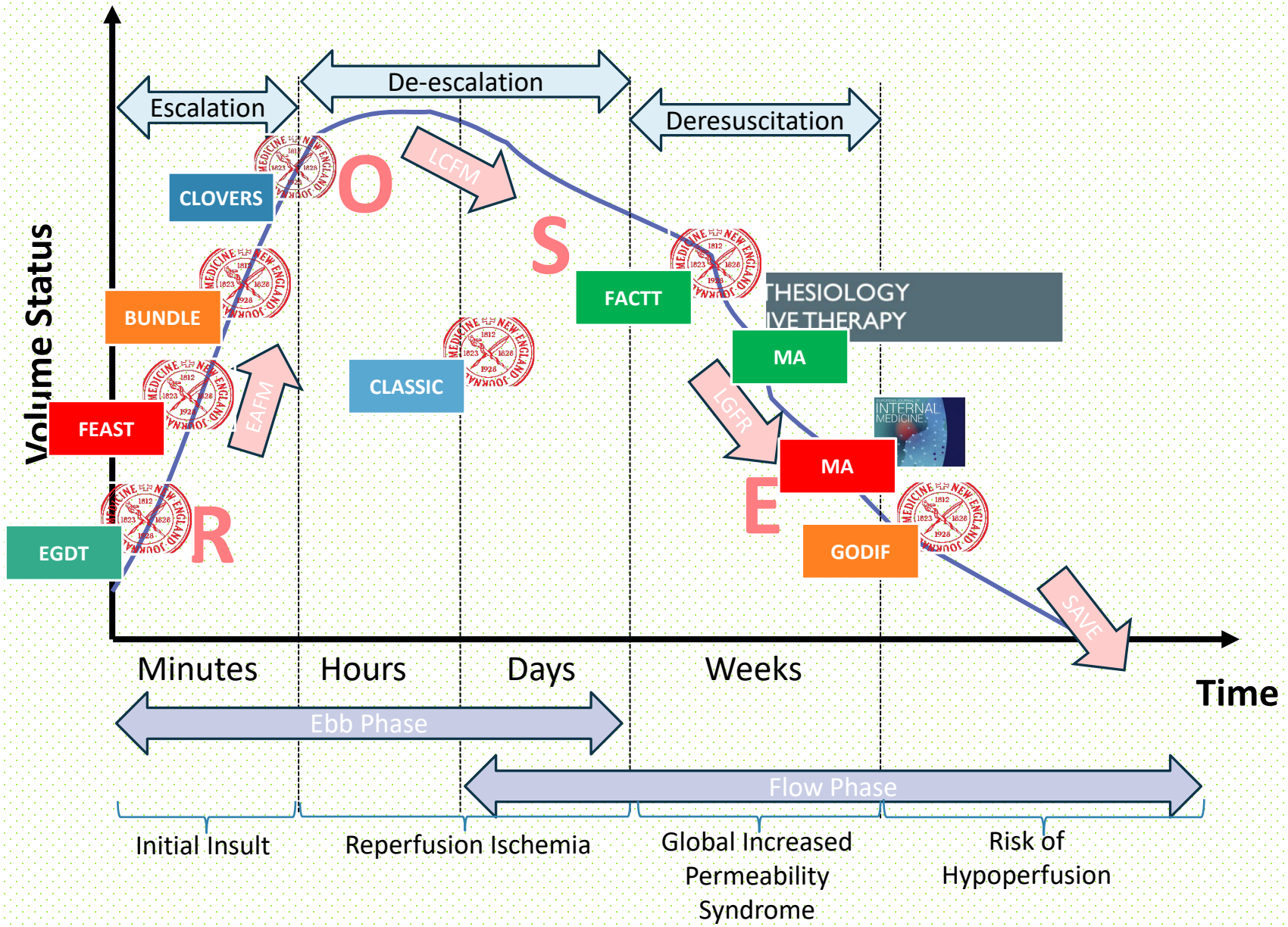
Test for overall effect: Z = 6.20 ($P < 0.00001$)



Forest plot looking at the effect of a restrictive compared to a liberal fluid regimen on mortality.



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

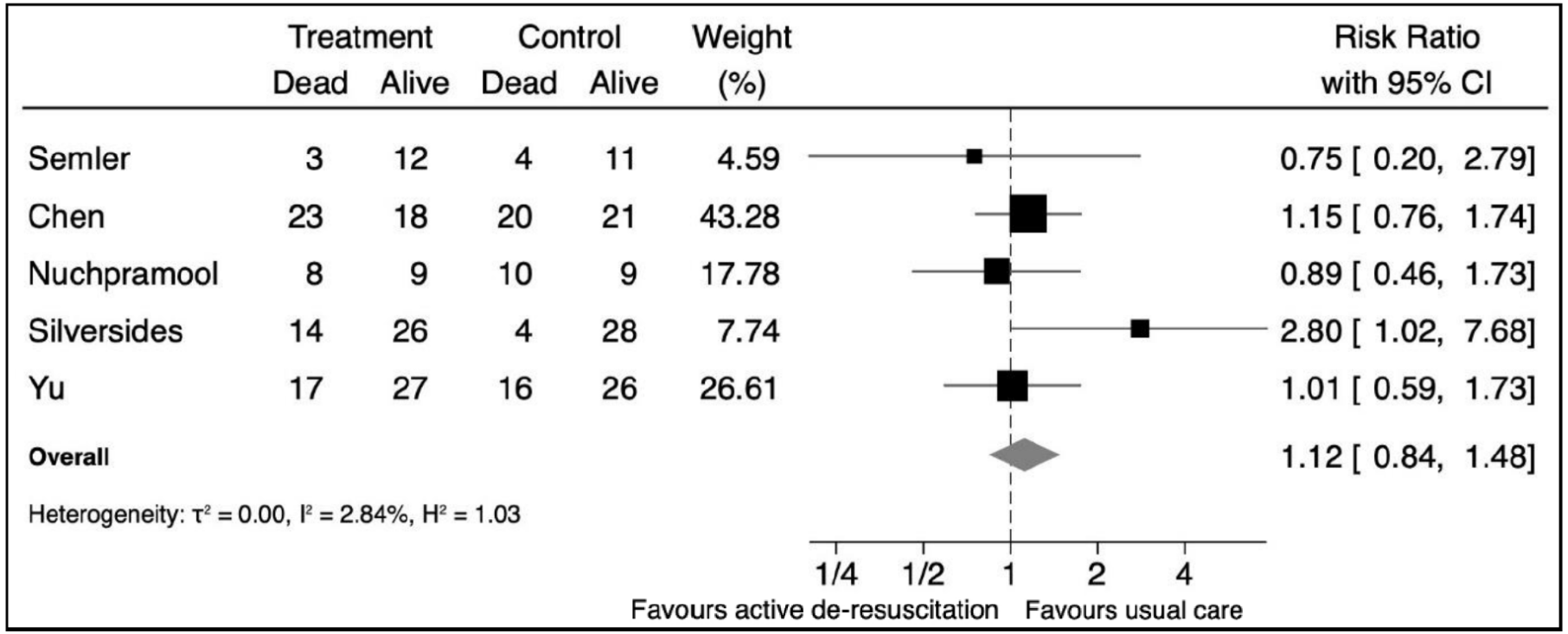
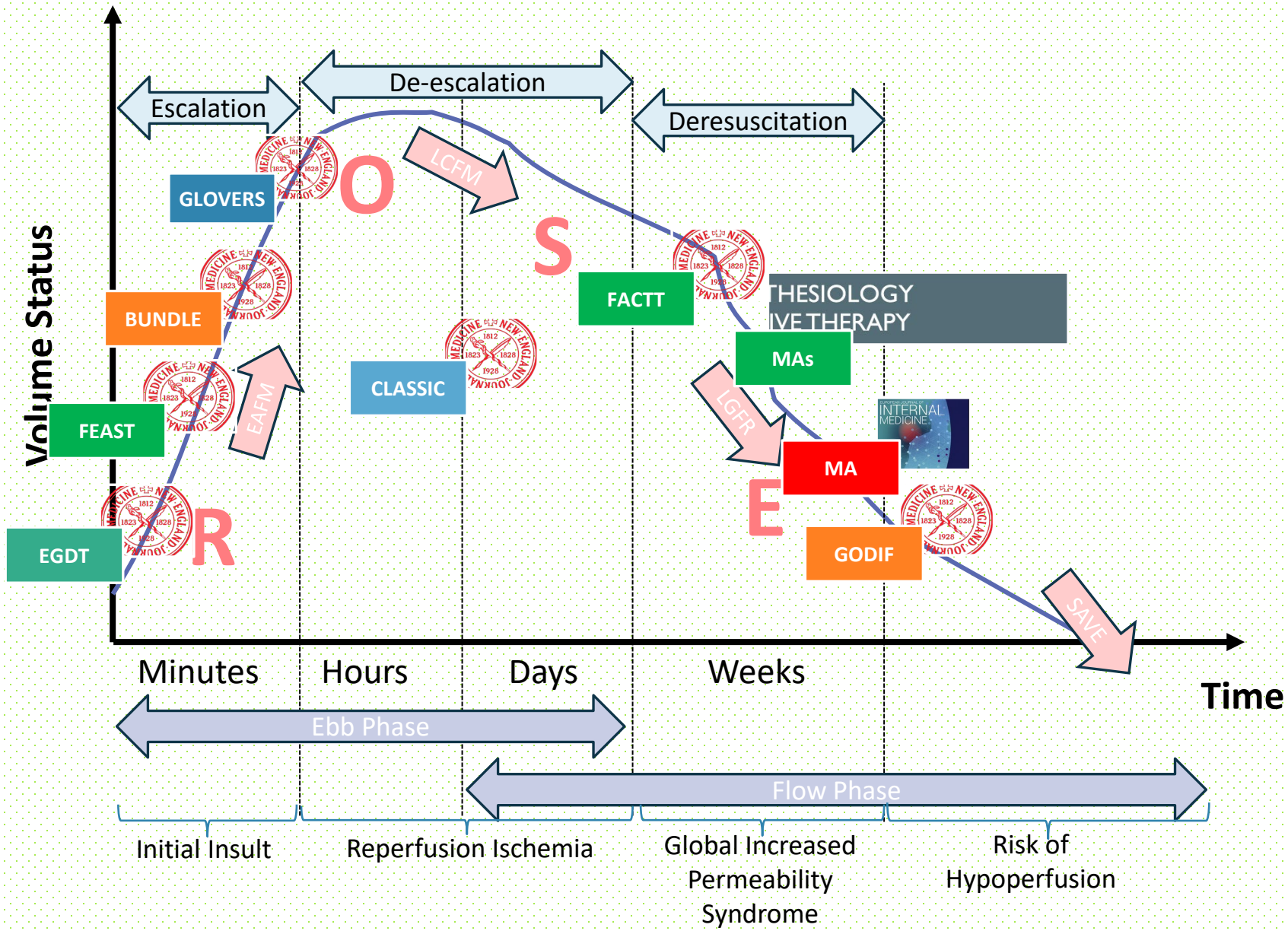


Fig. 2. Active de-resuscitation and short-term mortality.



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

acta Anaesthesiologica Scandinavica
An international journal of anaesthesiology, intensive care, pain, and critical emergency medicine
ssai

RESEARCH ARTICLE | Open Access

The clinical trial was stopped early due to imprecise fluid balance assessment!

blinded trial (GODIF trial—First version)

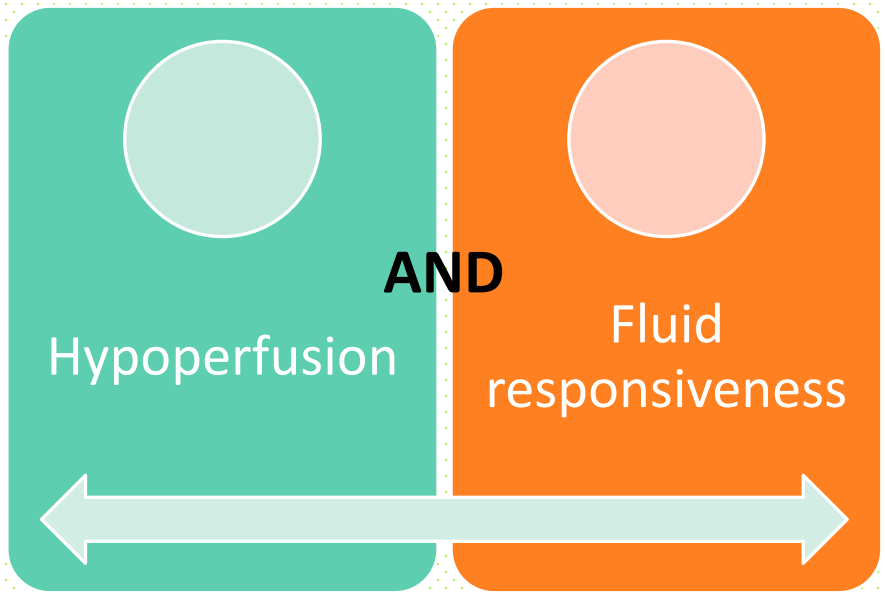
Sine Wichmann, Martin Schønemann-Lund, Anders Perner, Theis S. Itenov, Theis Lange, Christian Gluud, Rasmus E. Berthelsen, Anne C. Brøchner, Jørgen Wiis, Morten H. Bestle

First published: 12 January 2023 | https://doi.org/10.1111/aas.14196

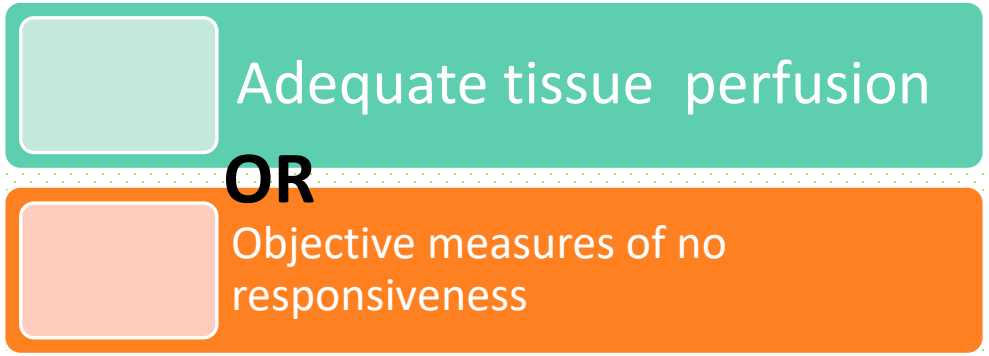
Current Evidence is Limited by the:

- Lack of high-quality RCTs
- Small sample sizes
- Heterogeneity of patient's population
- Heterogeneity of the applied de-resuscitation technique

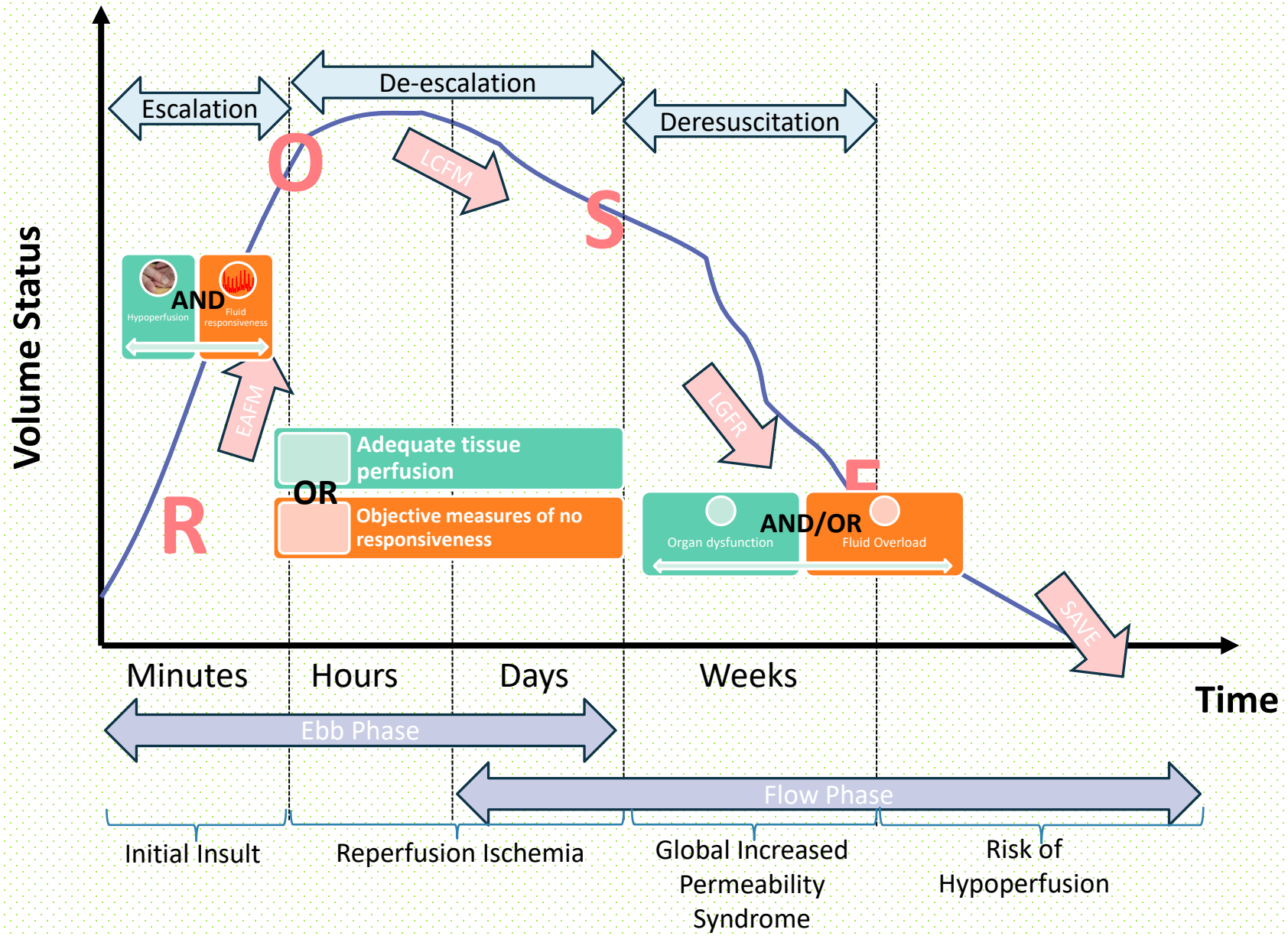
A reasonable approach is to limit fluid administration to patients with objective markers of:



De-escalate for organ rescue and support



De-resuscitate



EAFM, early adequate fluid management - LCFM: late conservative fluid management – LGFR: late goal directed fluid removal

Active Deresuscitation

- Combination therapy diuretics
- Application of PEEP
- Albumin 20% + diuretics
- PAL treatment: PEEP (=IAP) + albumin 20% + Lasix
- SLEDD with UF or SCUF
- CVVH with UF

Malbrain MLNG, Martin G, Ostermann M. Everything you need to know about deresuscitation. Intensive Care Med. 2022 Dec;48(12):1781-1786.

Questions?

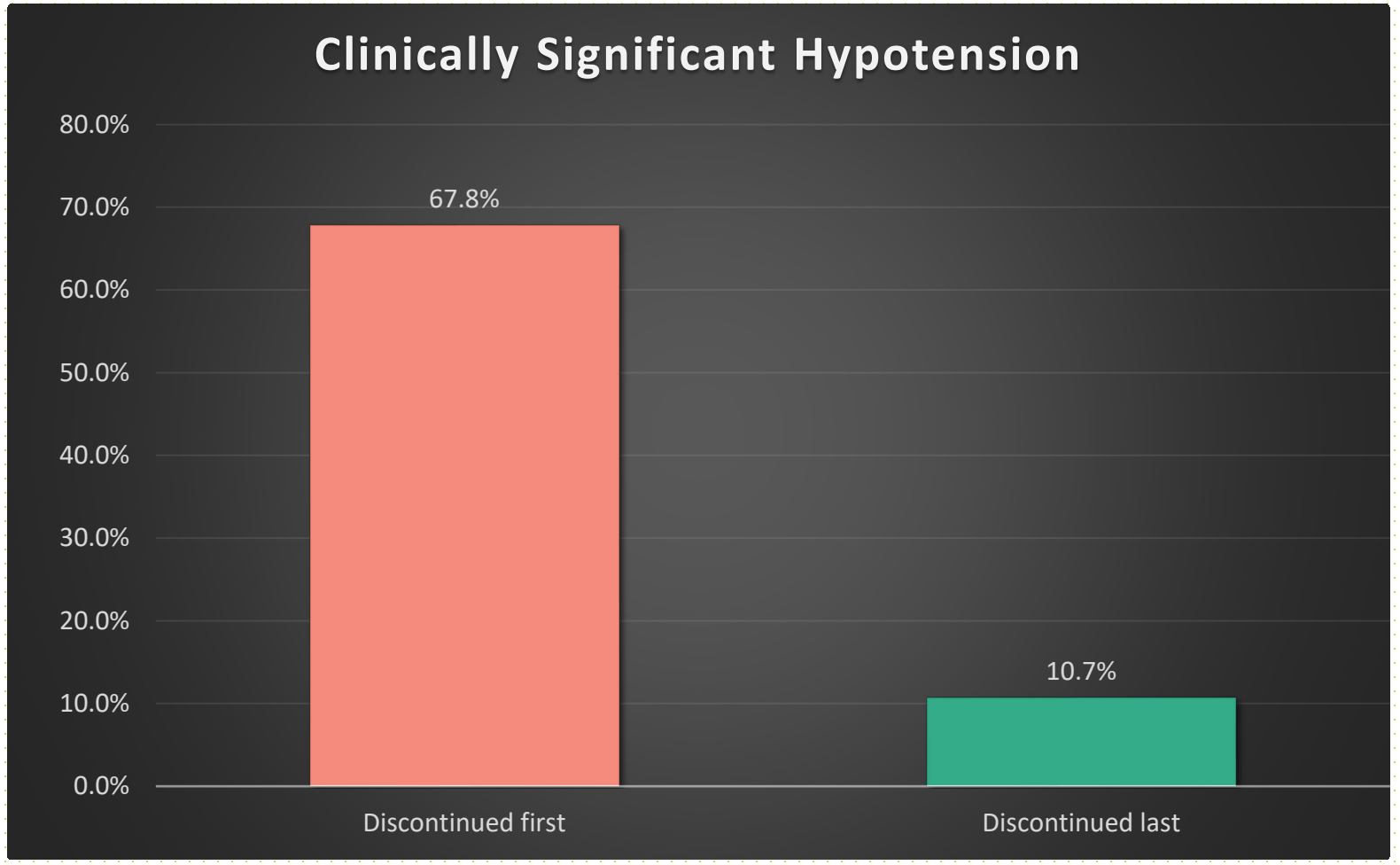
When should we start fluid de-resuscitation?

How should vasopressors be discontinued?

Should we tapper or discontinue steroids?

Can we guide antibiotic discontinuation based on procalcitonin?

Vasopressin Discontinuation



Hammond DA, et al. J Intensive Care Med. 2019 Oct;34(10):805-810.

Ann Pharmacother. 2018 Aug;52(8):733-739. doi: 10.1177/1060028018765187. Epub 2018 Mar 21.

Evaluating Vasopressor Discontinuation Strategies in Patients With Septic Shock on Concomitant Norepinephrine and Vasopressin Infusions

Nadine Musallam [1], Diana Altshuler [1], Cristian Merchan [1], Bishoy Zakhary [1], Caitlin Aberle [1], John Papadopoulos [1]

Vasopressin discontinuation first was associated with higher rate of hypotension (62.2% vs. 28.6%, P=0.004)

J Intensive Care Med. 2019 Sep;34(9):761-765. doi: 10.1177/0885066617716396. Epub 2017 Jul 28.

Hemodynamic Instability Secondary to Vasopressin Withdrawal in Septic Shock

Brittany D Bissell [1 2], Carolyn Magee [1], Peter Moran [2], Melissa L Thompson Bastin [1 2], Alexander H Flannery [1 2]

Significant increase in hemodynamic instability (74% vs 16.7%, P < .01) in 61 patients retrospectively

Questions?

When should we start fluid de-resuscitation?

How should vasopressors be discontinued?

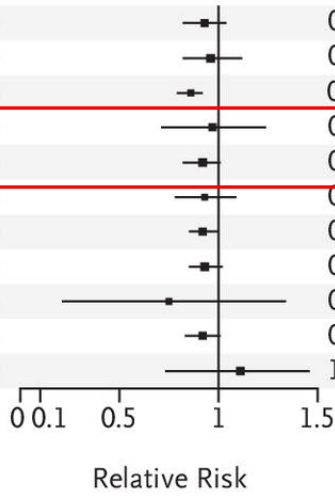
Should we tapper or discontinue steroids?

Can we guide antibiotic discontinuation based on procalcitonin?

Taper or Abrupt?

A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



Questions?

When should we start fluid de-resuscitation?

How should vasopressors be discontinued?

Should we tapper or discontinue steroids?

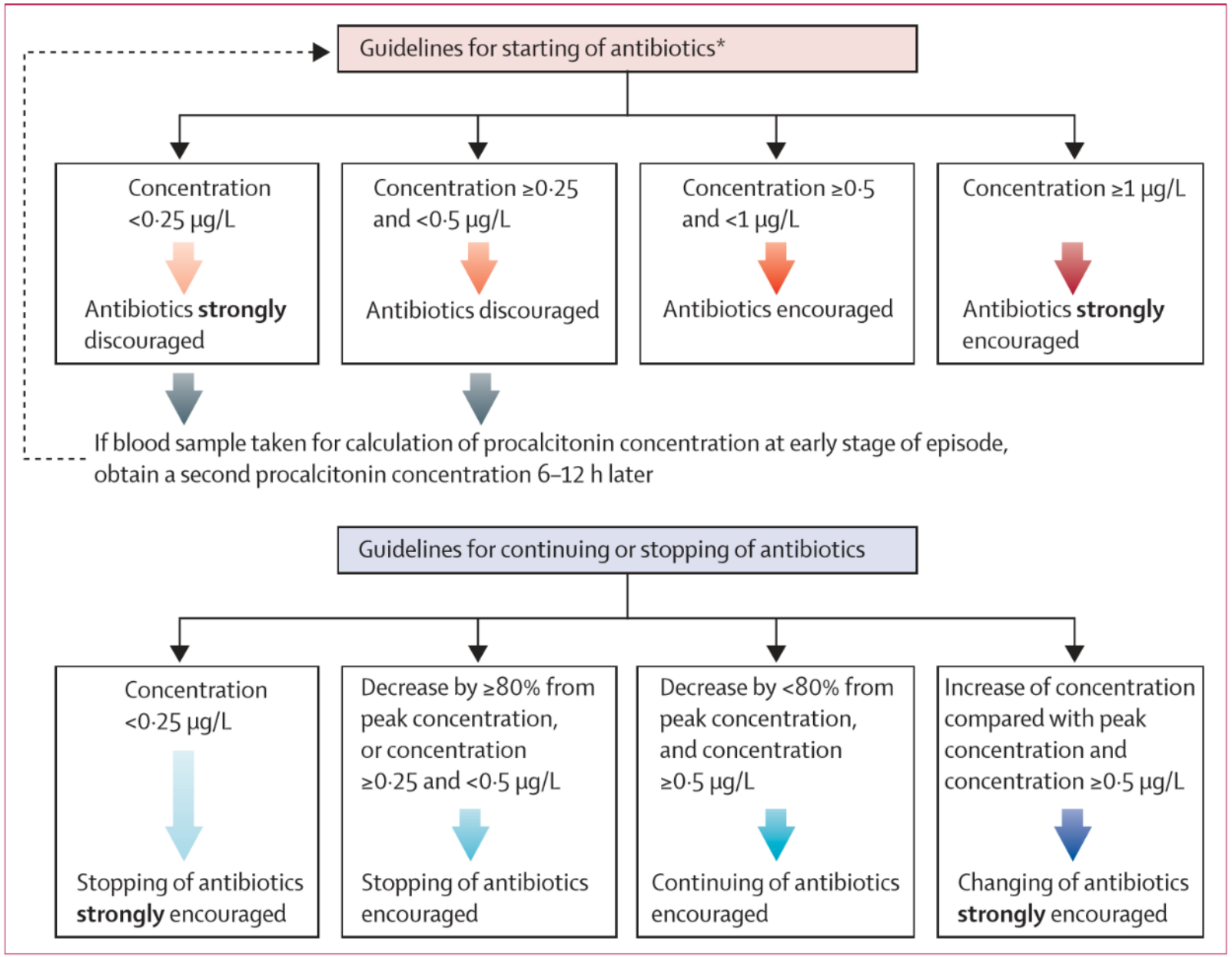
Can we guide antibiotic discontinuation based on procalcitonin?

THE LANCET

Articles

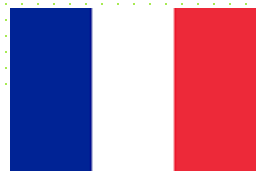
Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Lila Bouadma, Charles-Edouard Luyt, Florence Tubach, Christophe Cracco, Antonio Alvarez, Carole Schwebel, Frédérique Schortgen, Sigismond Lasocki, Benoît Veber, Monique Dehoux, Maguy Bernard, Blandine Pasquet, Bernard Régnier, Christian Brun-Buisson, Jean Chastre, Michel Wolff,* for the PRORATA trial group†*



Bouadma L.et al. Lancet 2010; 375:463–74.

Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial)



Multicenter, prospective, parallel-group, open-label trial Critically ill patients with suspected bacterial infections in seven intensive care units June, 2007, and May, 2008			
	Procalcitonin	**Control**	**Absolute difference (90% CI)**
# of Patients	307	314	NA
# days without antibiotic	14·3 days [SD 9·1]	11·6 days [SD 8·2]	2·7 days (1·4 to 4·1)
28-day Mortality	**21·2%**	**20.4%**	**0·8% (4·6 to 6·2)**
60-daymortality	**30·0%**	**26.1%**	**3·8% (2·1 to 9·7)**

√ $p = 0.0001$

Bouadma L.et al. Lancet 2010; 375:463–74.

THE LANCET

Articles

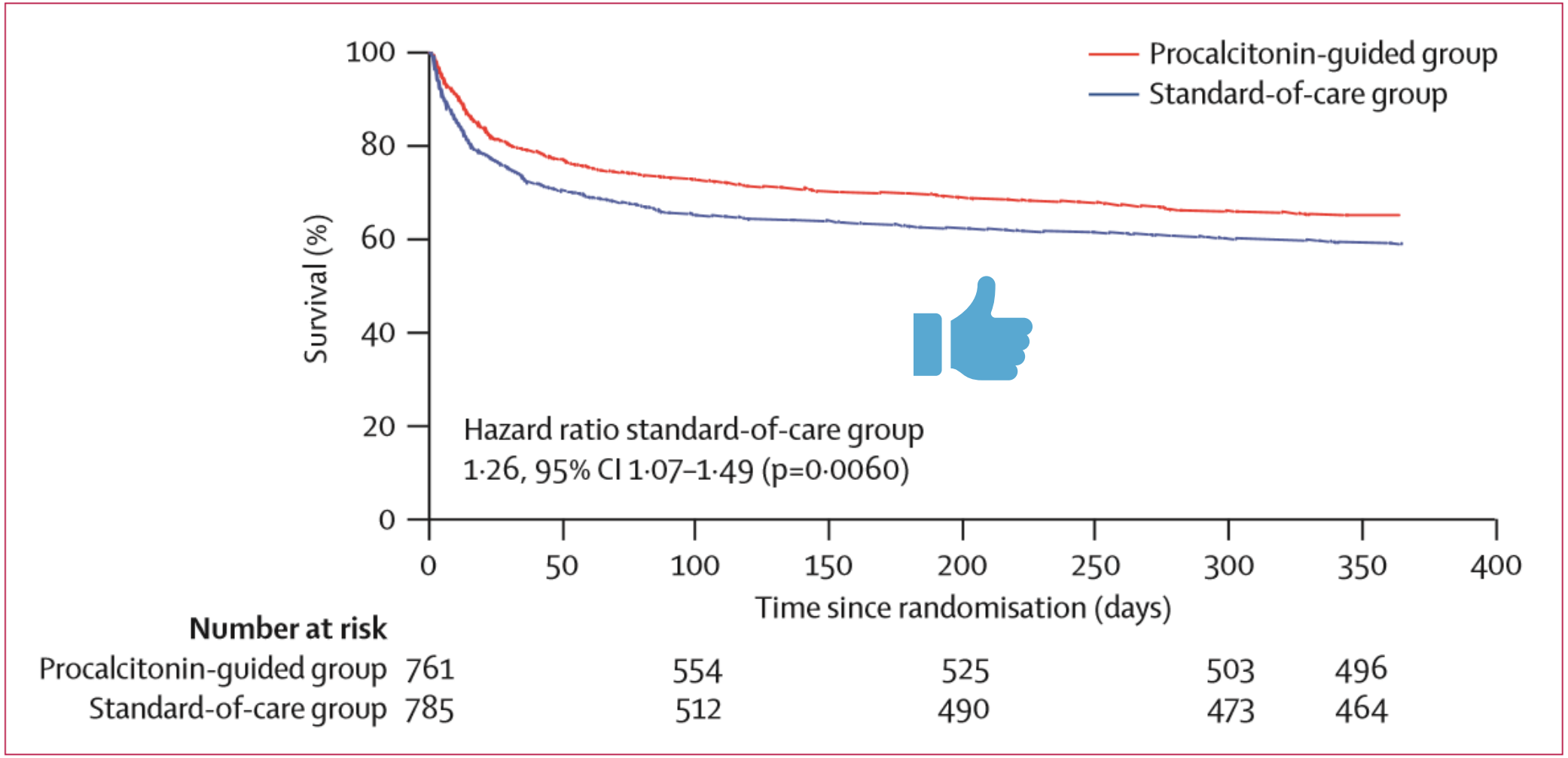
Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

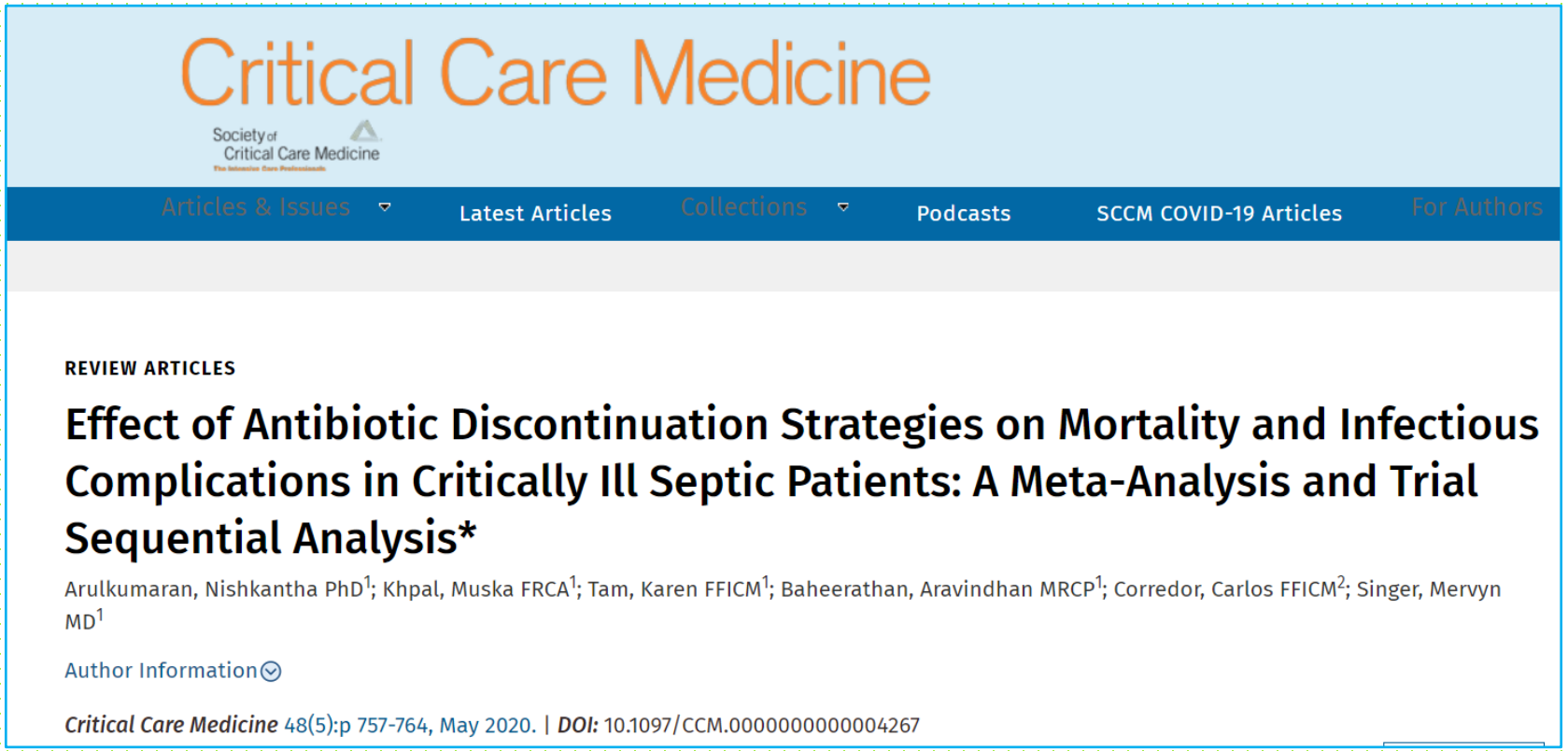
Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomized, controlled, open-label trial

Prospective, multicentre, randomized, controlled, open-label intervention trial
Adult critically ill patients in 15 hospitals in the Netherlands

	Procalcitonin	Control	Absolute difference (90% CI)	
# of Patients	761	785	NA	
Antibiotic daily defined doses	7·5 (IQR 4·0–12·7)	19·3 (5·0–16·6)	2·69 (1·26–4·12)	√ $p < 0.0001$
Duration of antibiotic treatment	**5 days (3–9)**	**7 days (4–11)**	**1·22 (0·65–1·78)**	√ $p < 0.0001$



The Lancet Infectious Diseases



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REVIEW ARTICLES

Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis*

Arulkumaran, Nishkantha PhD[1]; Khpal, Muska FRCA[1]; Tam, Karen FFICM[1]; Baheerathan, Aravindhan MRCP[1]; Corredor, Carlos FFICM[2]; Singer, Mervyn MD[1]

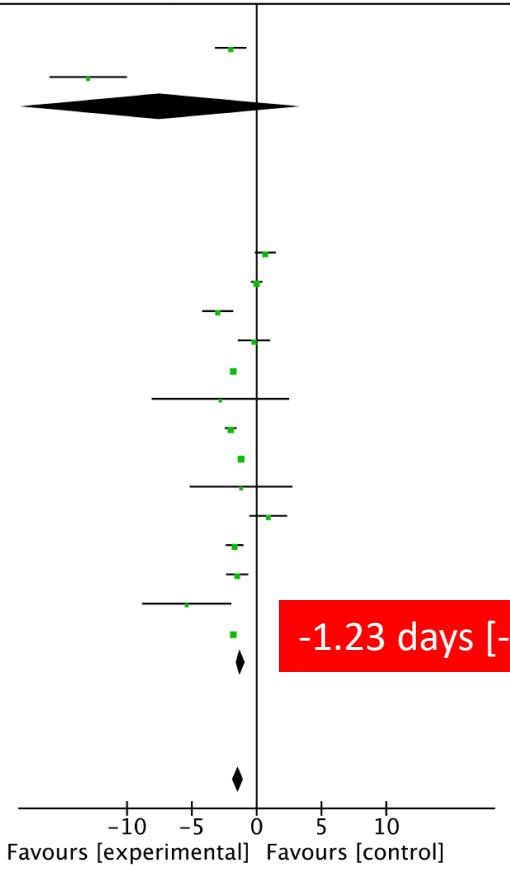
Author Information

Critical Care Medicine 48(5):p 757-764, May 2020. | **DOI:** 10.1097/CCM.0000000000004267

Arulkumaran, N. et al. Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis. Critical Care Medicine 48(5):p 757-764, May 2020.

Duration of Antibiotics

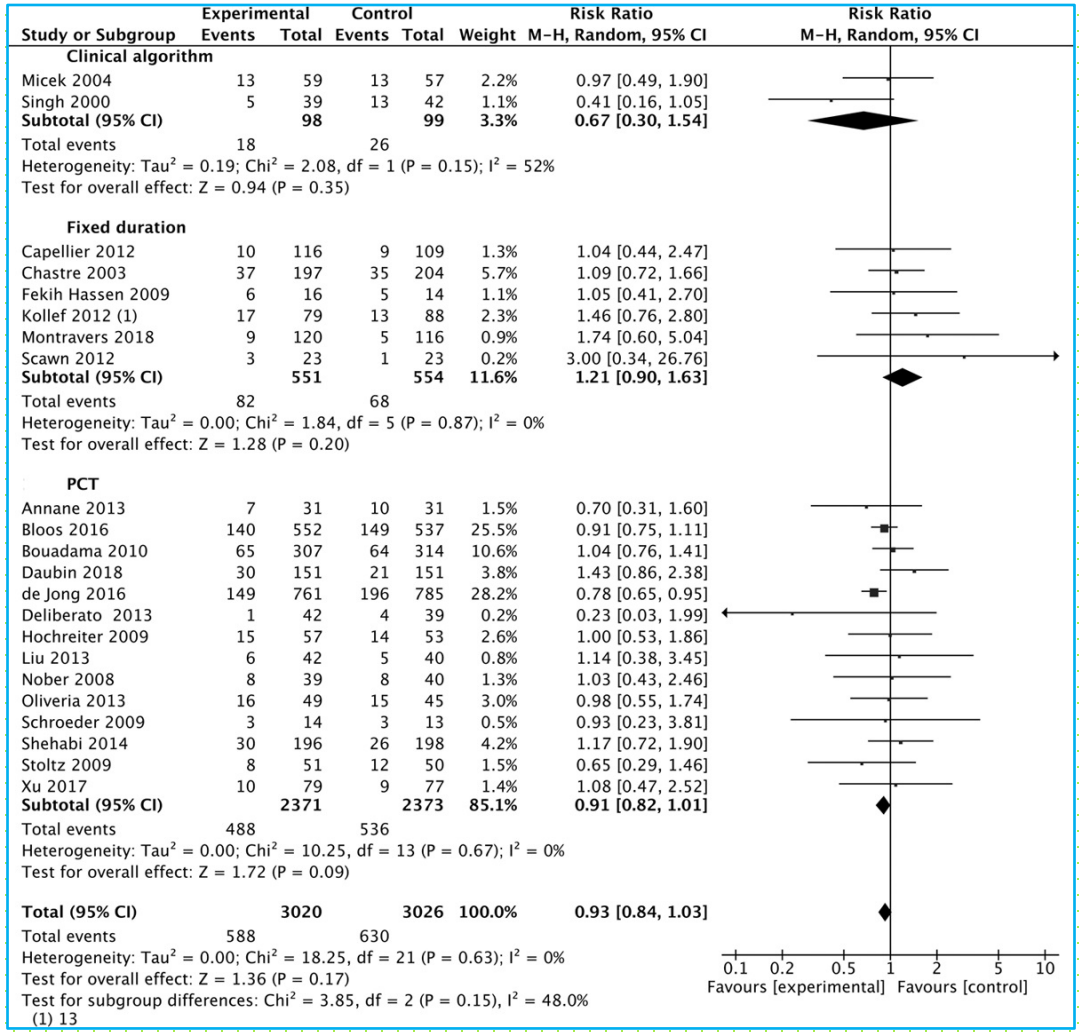
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Clinical algorithm								
Micek 2004	6	4.9	150	8	5.6	140	5.6%	−2.00 [−3.21, −0.79]
Singh 2000	3	0.2	39	16	9.9	42	1.6%	−13.00 [−15.99, −10.01]
Subtotal (95% CI)			**189**			**182**	**7.2%**	**−7.41 [−18.19, 3.37]**
Heterogeneity: Tau^2 = 59.14; Chi^2 = 44.51, df = 1 (P < 0.00001); I^2 = 98%								
Test for overall effect: Z = 1.35 (P = 0.18)								
PCT								
Annane 2013	4.67	0.7	31	4	2.2	31	7.6%	0.67 [−0.14, 1.48]
Bloos 2016	8.5	3.8	552	8.5	3.8	537	9.6%	0.00 [−0.45, 0.45]
Bouadama 2010	10.3	7.7	307	13.3	7.6	314	5.6%	−3.00 [−4.20, −1.80]
Daubin 2018	5.2	6.5	151	5.4	4.4	151	5.4%	−0.20 [−1.45, 1.05]
de Jong 2016	5.5	1.7	761	7.3	2	785	10.6%	−1.80 [−1.98, −1.62]
Deliberato 2013	15.5	10.4	42	18.3	13.6	39	0.6%	−2.80 [−8.10, 2.50]
Hochreiter 2009	5.9	1.7	57	7.9	0.5	53	9.5%	−2.00 [−2.46, −1.54]
Liu 2013	8.1	0.3	42	9.3	0.3	40	10.7%	−1.20 [−1.33, −1.07]
Nober 2008	12.3	9	39	13.5	9	40	1.0%	−1.20 [−5.17, 2.77]
Oliveria 2013	8.1	3.7	49	7.2	3.5	45	4.6%	0.90 [−0.56, 2.36]
Schroeder 2009	6.6	1.1	14	8.3	0.7	13	8.3%	−1.70 [−2.39, −1.01]
Shehabi 2014	11	4.1	196	12.5	4.6	198	7.3%	−1.50 [−2.36, −0.64]
Stoltz 2009	10.6	7.6	51	16	9.9	50	1.3%	−5.40 [−8.85, −1.95]
Xu 2017	8.3	0.3	79	10.1	0.4	77	10.7%	−1.80 [−1.91, −1.69]
Subtotal (95% CI)			**2371**			**2373**	**92.8%**	**−1.23 [−1.61, −0.85]**
Heterogeneity: Tau^2 = 0.30; Chi^2 = 157.98, df = 13 (P < 0.00001); I^2 = 92%								
Test for overall effect: Z = 6.38 (P < 0.00001)								
Total (95% CI)			**2560**			**2555**	**100.0%**	**−1.46 [−1.87, −1.05]**
Heterogeneity: Tau^2 = 0.41; Chi^2 = 214.77, df = 15 (P < 0.00001); I^2 = 93%								
Test for overall effect: Z = 6.95 (P < 0.00001)								
Test for subgroup differences: Chi^2 = 1.26, df = 1 (P = 0.26), I^2 = 20.7%								



-1.23 days [-1.61-0.85]

Arulkumaran, N. et al. Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis. Critical Care Medicine 48(5):p 757-764, May 2020.

Mortality



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Clinical algorithm						
Micek 2004	13	59	13	57	2.2%	0.97 [0.49, 1.90]
Singh 2000	5	39	13	42	1.1%	0.41 [0.16, 1.05]
Subtotal (95% CI)		**98**		**99**	**3.3%**	**0.67 [0.30, 1.54]**
Total events	18		26			
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.08$, df = 1 (P = 0.15); $I^2 = 52\%$						
Test for overall effect: Z = 0.94 (P = 0.35)						
Fixed duration						
Capellier 2012	10	116	9	109	1.3%	1.04 [0.44, 2.47]
Chastre 2003	37	197	35	204	5.7%	1.09 [0.72, 1.66]
Fekih Hassen 2009	6	16	5	14	1.1%	1.05 [0.41, 2.70]
Kollef 2012 (1)	17	79	13	88	2.3%	1.46 [0.76, 2.80]
Montravers 2018	9	120	5	116	0.9%	1.74 [0.60, 5.04]
Scawn 2012	3	23	1	23	0.2%	3.00 [0.34, 26.76]
Subtotal (95% CI)		**551**		**554**	**11.6%**	**1.21 [0.90, 1.63]**
Total events	82		68			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.84$, df = 5 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 1.28 (P = 0.20)						
PCT						
Annane 2013	7	31	10	31	1.5%	0.70 [0.31, 1.60]
Bloos 2016	140	552	149	537	25.5%	0.91 [0.75, 1.11]
Bouadama 2010	65	307	64	314	10.6%	1.04 [0.76, 1.41]
Daubin 2018	30	151	21	151	3.8%	1.43 [0.86, 2.38]
de Jong 2016	149	761	196	785	28.2%	0.78 [0.65, 0.95]
Deliberato 2013	1	42	4	39	0.2%	0.23 [0.03, 1.99]
Hochreiter 2009	15	57	14	53	2.6%	1.00 [0.53, 1.86]
Liu 2013	6	42	5	40	0.8%	1.14 [0.38, 3.45]
Nober 2008	8	39	8	40	1.3%	1.03 [0.43, 2.46]
Oliveria 2013	16	49	15	45	3.0%	0.98 [0.55, 1.74]
Schroeder 2009	3	14	3	13	0.5%	0.93 [0.23, 3.81]
Shehabi 2014	30	196	26	198	4.2%	1.17 [0.72, 1.90]
Stoltz 2009	8	51	12	50	1.5%	0.65 [0.29, 1.46]
Xu 2017	10	79	9	77	1.4%	1.08 [0.47, 2.52]
Subtotal (95% CI)		**2371**		**2373**	**85.1%**	**0.91 [0.82, 1.01]**
Total events	488		536			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.25$, df = 13 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**3020**		**3026**	**100.0%**	**0.93 [0.84, 1.03]**
Total events	588		630			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.25$, df = 21 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: $Chi^2 = 3.85$, df = 2 (P = 0.15), $I^2 = 48.0\%$						
(1) 13						

No effect on mortality

Arulkumaran, N. et al. Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis*. Critical Care Medicine 48(5):p 757-764, May 2020.

Society of Critical Care Medicine
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Recommendation

31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.
Weak recommendation, low quality of evidence.

Evans, L. et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine 49(11):p e1063-e1143, November 2021

What would your approach be for this patient? (check all what apply)?

- ❑ Start diuresis and aim for negative fluid balance
- ❑ Wean norepinephrine first before stopping vasopressin
- ❑ Stop antibiotics once procalcitonin is down by 80%
- ❑ Discontinue hydrocortisone without tapering once off the vasopressors

Take Home Message

In patients recovering from sepsis and septic sho

- Know when give, stop, and remove fluid
- Consider discontinuation of norepinephrine first
- No need for steroid taper
- May use procalcitonin as a biomarker for antibiotic discontinuation

Thank you

www.icureach.com