Drier is Better: Fluid De-resuscitation in Critically Ill Adults

A Presentation for HealthTrust Members
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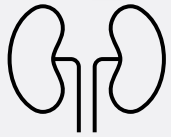
Financial Disclosure

Drs. Kennedy and Blackwell have no relevant relationships with ineligible companies to disclose.

Note: This program may contain the mention of drugs, brands, or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand, product, service, or supplier.

Learning Objectives for Pharmacists & Nurses

Recall the risks of volume overload in critically ill patients

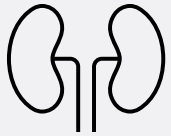


Identify the principles of fluid de-resuscitation in critically ill patients

Recognize patients who may benefit from fluid de-resuscitation to improve outcomes

Learning Objectives for Pharmacy Technicians

Recall the risks of volume overload in critically ill patients



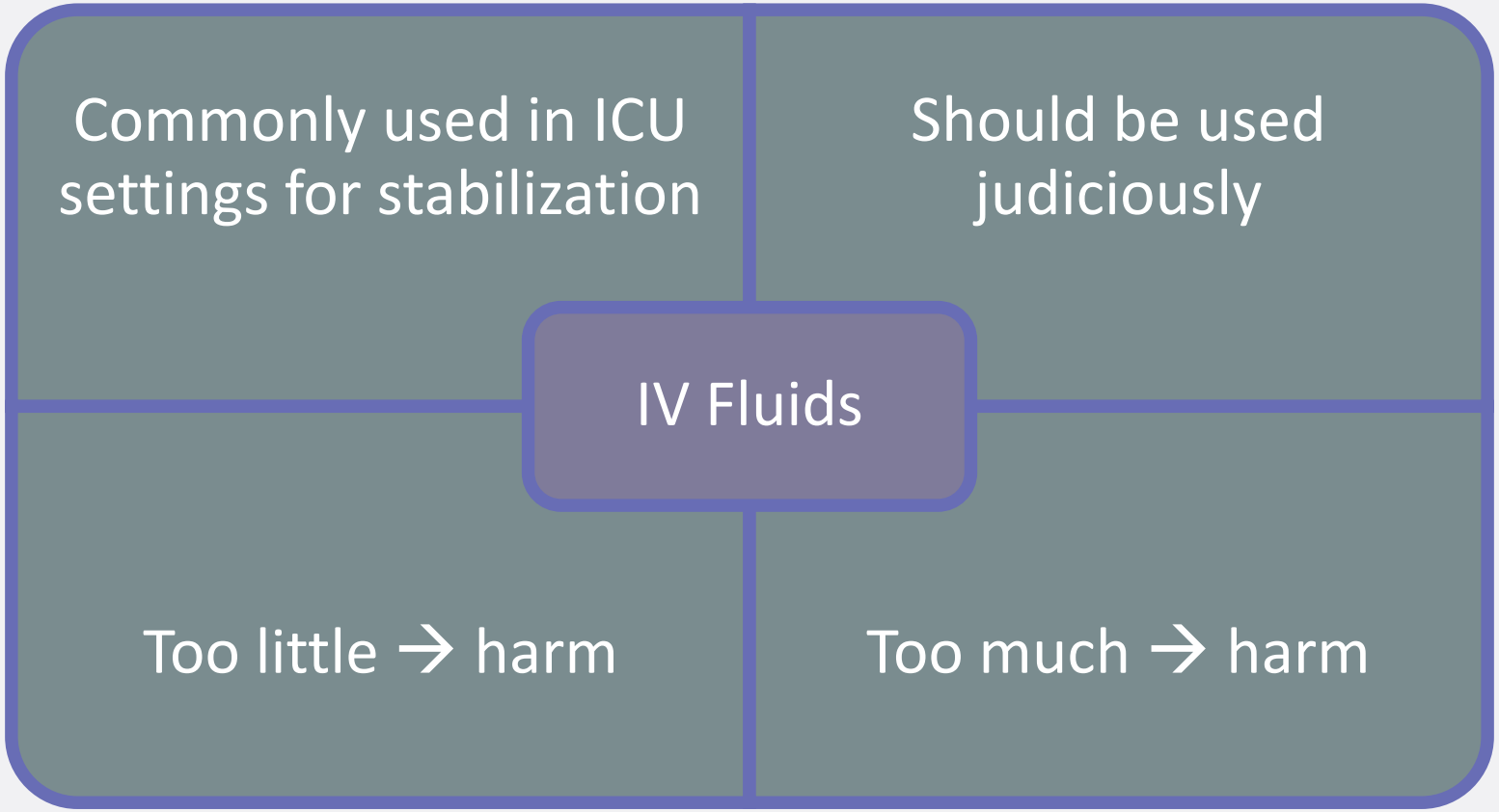
Identify the medications commonly used for fluid de-resuscitation in critically ill patients

Recognize the storage and preparation considerations for medications used for fluid de-resuscitation in critically ill patients

Abbreviations

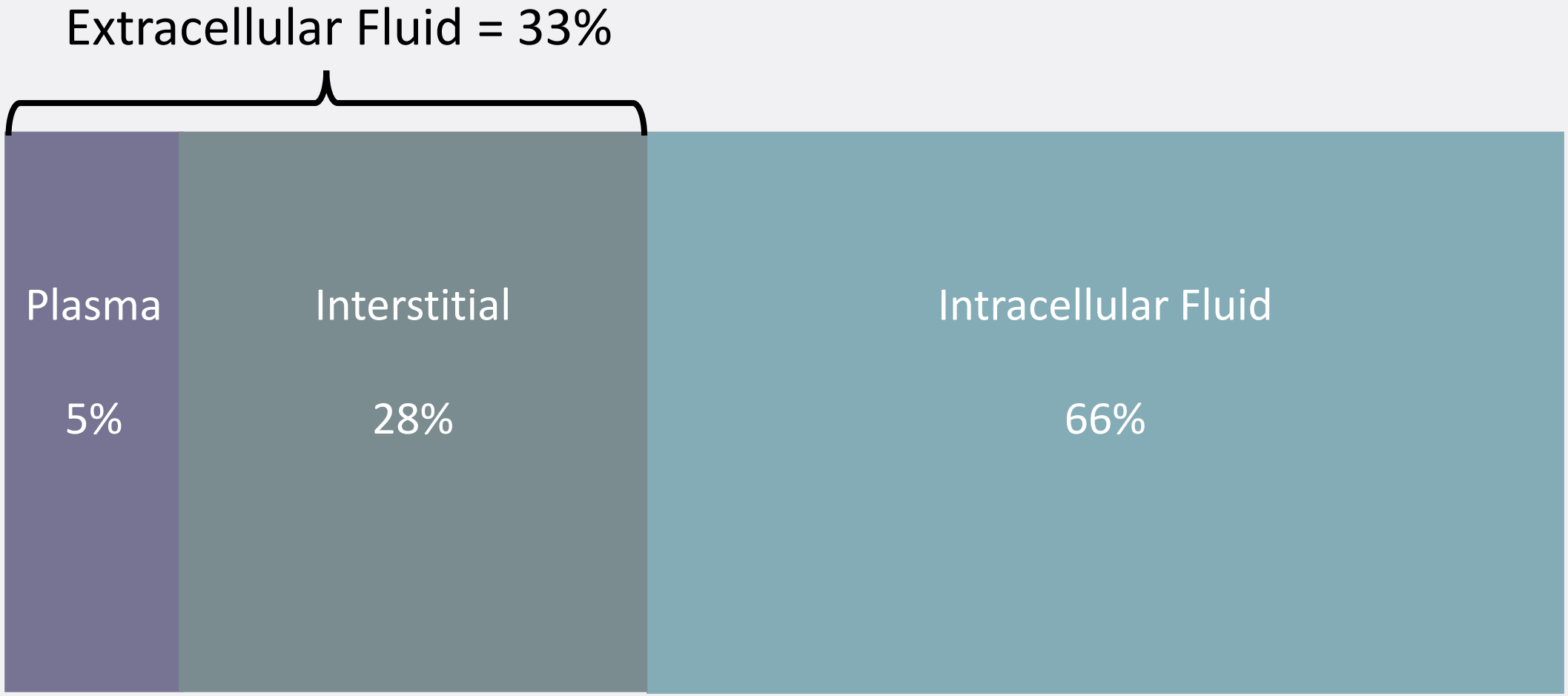
- Adverse drug events
- AKI: acute kidney injury
- BNP: basic natriuretic peptide
- CFB: cumulative fluid balance
- CI: cardiac index
- CKD: chronic kidney disease
- CO: cardiac output
- CVP: central venous pressure
- IAP: intraabdominal pressure
- KDIGO: Kidney Disease: Improving Global Outcomes
- LA: lactic acid
- LOS: length of stay
- MAP: mean arterial pressure
- PLR: passive leg raise
- PO: by mouth
- PPV: pulse pressure variation
- RCT: randomized controlled trial
- RRT: renal replacement therapy
- $ScvO_2$: central venous oxygen saturation
- SOFA: Sequential Organ Failure Assessment
- SSC: Surviving Sepsis Campaign
- SV: stroke volume
- UOP: urine output

IV Fluid Use in Critical Care



Source: *Crit Care Med*. 2023;51(10):1397-1406

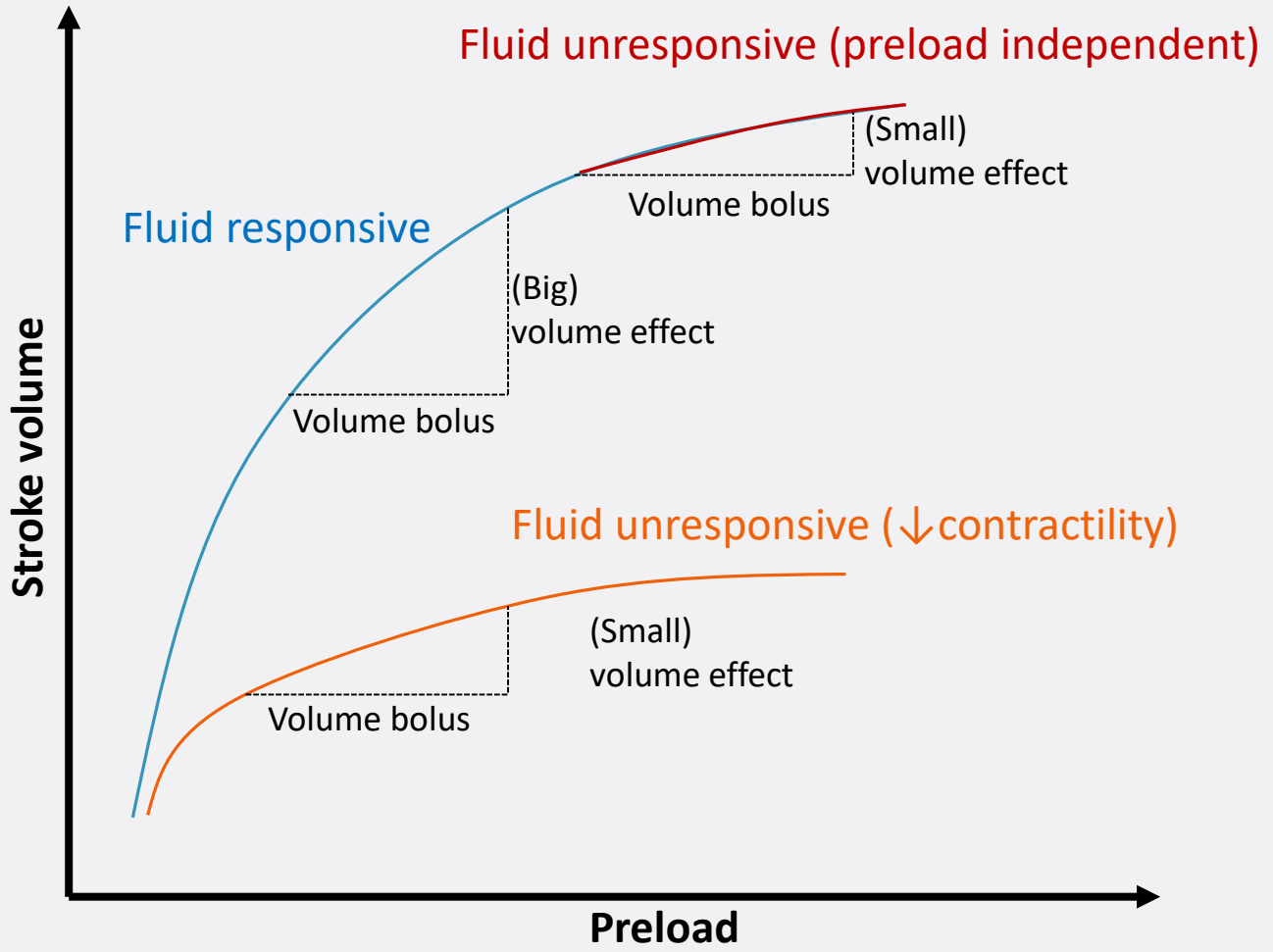
Fluid Compartments



Source: *Crit Care Med*. 2023;51(10):1397-1406

Physiologic Response to Fluids

- Response to therapy depends on cardiac function and baseline preload
  - Decreased contractility → fluid unresponsive
  - Plateau of the Starling curve



Source: *Nephrol Dial Transplant*. 2023;38(7):1603-1612

Sources of Fluids

Intentional

Boluses
Maintenance
Nutrition

"Creep"/Hidden

Flushes
Medication diluents
Blood products

Source: *Ann Intensive Care*. 2019;9(1):132

SUFFIR

Objective	• Identify sources of fluid administration during acute phase of resuscitation • Describe proportion of resuscitation and non-resuscitation fluids • Assess associations between center practices and fluid intake
Design	Prospective multicenter cohort
Population (n=284)	Requiring vasopressor(s) and/or invasive mechanical ventilation
Measurements	All fluids administered IV or enteral lines recorded over 24 hours

Sources: *Ann Intensive Care*. 2019;9(1):132
Crit Care Med. 2024;52(2):258-267

SUFFIR

Indisputable homeostasis goal

Fluid losses, rehydration, nutrition, blood products

Drug carriers

Vasopressors, antibiotics, sedation, analgesics

Maintenance fluids

Insensible losses

Fluids for technical needs

Vascular access management, keep vein open, vehicle, RRT

Source: *Crit Care Med*. 2024;52(2):258-267

SUFFIR

Total fluid (L), median [IQR]	3.5 [2.4, 4.9]
Indisputable	36% of total
Maintenance	28% of total
Drug carriers	22% of total
Technical needs	5% of total

Fluid boluses → only 14% of total volume

Source: *Crit Care Med*. 2024;52(2):258-267

Definitions

Fluid overload → 10% weight increase due to fluid accumulation

Fluid accumulation → Overhydration associated with adverse clinical impact

Sources: *Intensive Care Med*. 2022;48(12):1781-1786
Br J Anaesth. 2014;113(5):740-747

Risks of Volume Overload

Relationship with positive fluid balance and unfavorable outcomes described in multiple studies

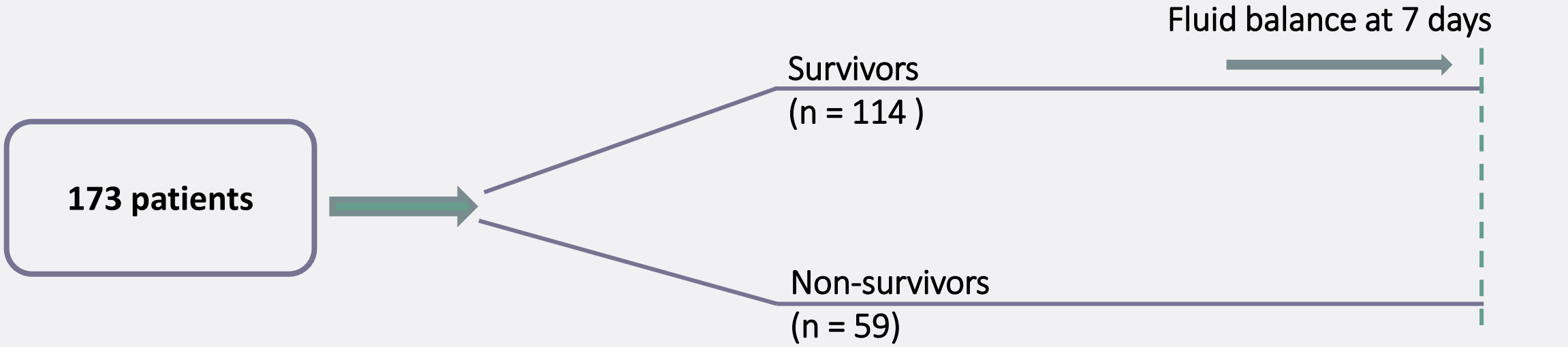
SOAP study → positive fluid balance among the strongest prognostic factors for death

Boyd, et al. → positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock

Sources: *Crit Care Med*. 2006;34(2):344-353
Crit Care Med. 2011;39(2):259-265

Archeampong et al.

Objective	To analyze if a positive fluid balance and its persistence over time was an independent prognostic factor in septic patients
Design	Prospective observational study
Inclusion	>15 years old, suspected or proven infection on antibiotics, SOFA ≥3, ICU admission ≥48 hours



Source: *Crit Care*. 2015;19(1):251

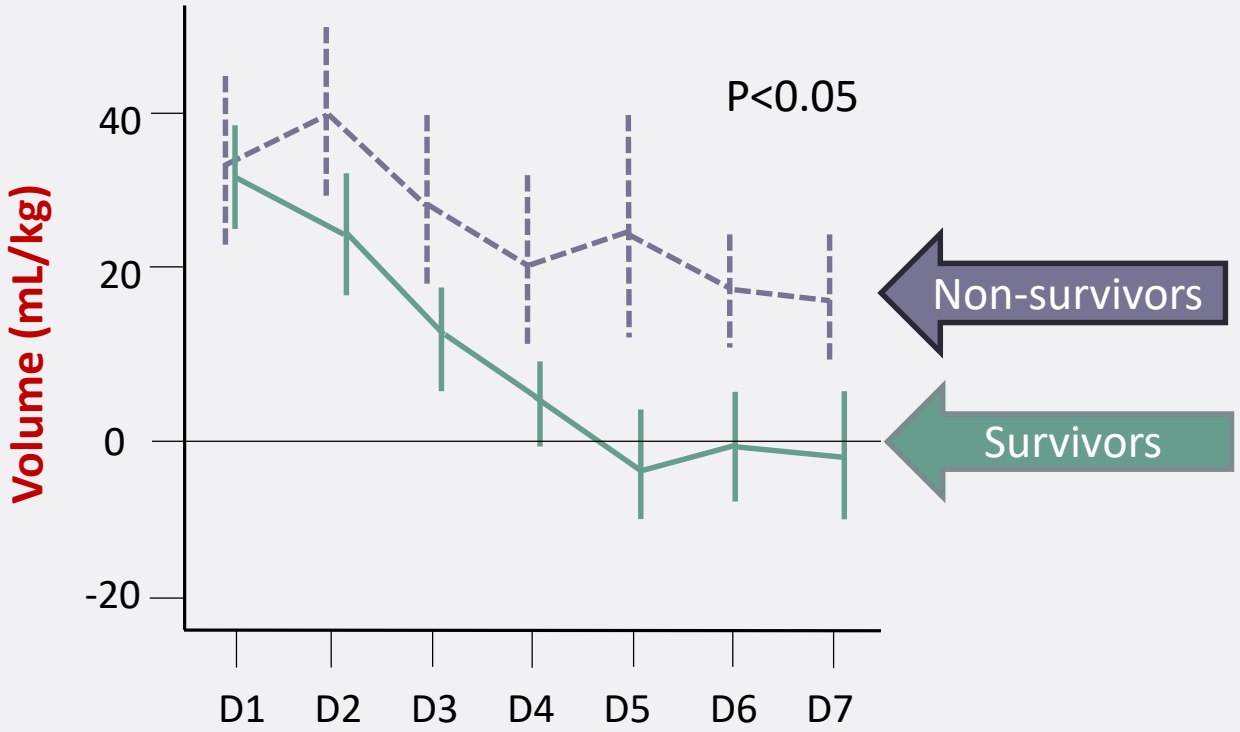
Archeampong et al.

Characteristics	Patients (n=173)	Non-survivors (n=59)	Survivors (n=114)	P value
Septic shock	135 (78)	57 (97)	78 (68)	<0.001
Duration of shock, days	3 ± 2	4 ± 2	2 ± 2	<0.001
SOFA score	8.2 ± 3.4	9 ± 3.3	7.7 ± 3.3	0.023
ICU LOS, days	6 [4, 10]	7 [4, 12]	6 [4, 8]	0.17
Data expressed as number (%), median [IQR], or mean ± SD				

Source: *Crit Care*. 2015;19(1):251

Archeampong et al.

Mean fluid balance (ml/kg) in survivors and non-survivors over the 7 days after sepsis onset



Conclusion

- Survivors were more likely to have a negative fluid balance early in their ICU stay
- Positive fluid balance was an independent prognostic factor for ICU mortality

Source: *Crit Care*. 2015;19(1):251

Fluid Stewardship

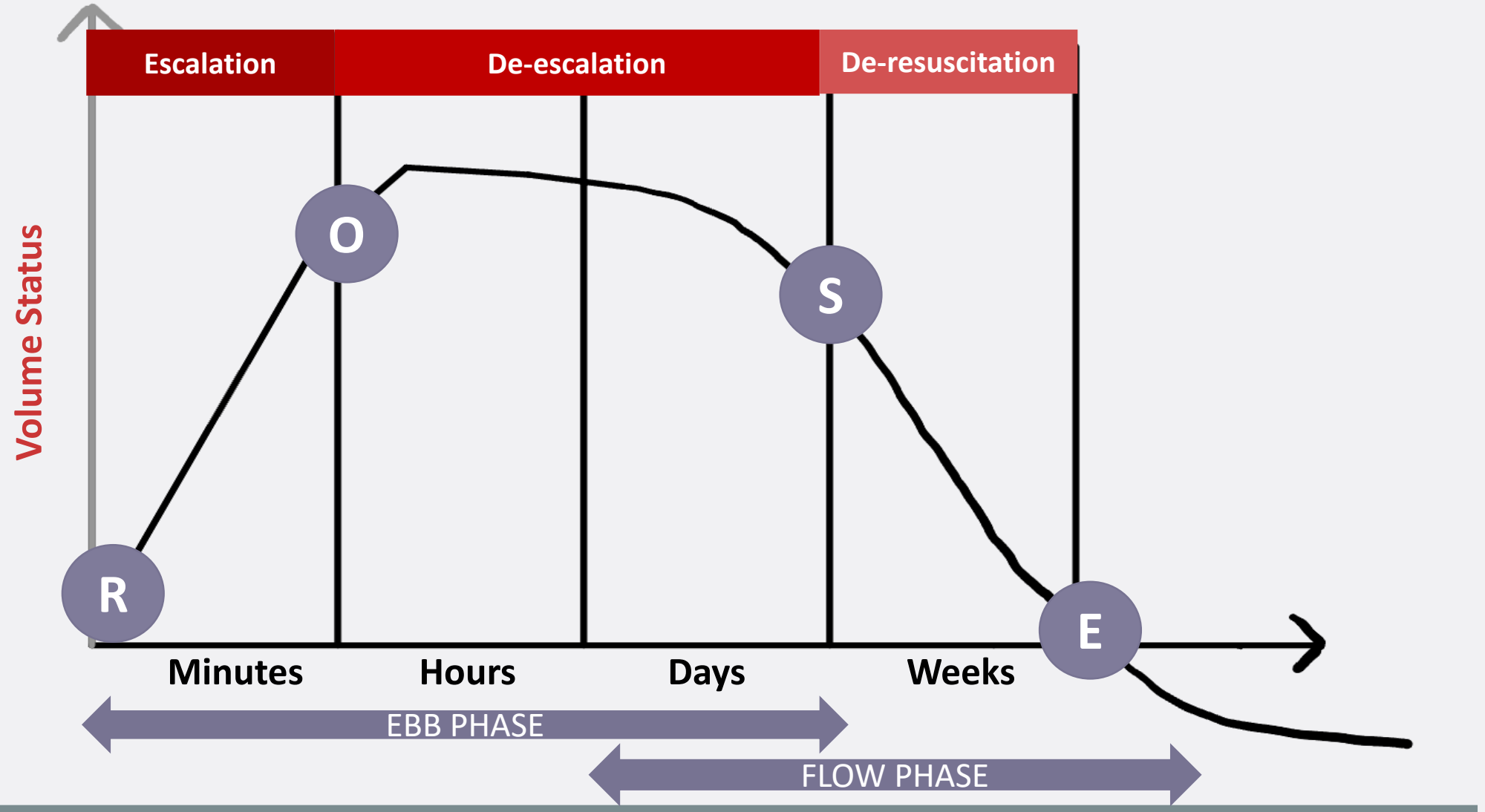
Rights → Drug, Patient, Route, Dose

Ds → Drug, Dose, Duration, De-escalation

ROSE → Resuscitation, Optimization, Stabilization, Evacuation

Source: *Am J Health Syst Pharm*. 2022;79(12):984-992

ROSE Model



Sources: *Intensive Care Med*. 2022;48(12):1781-1786
Ulus Cerrahi Derg. 2014;30(3):153-159
Ann Intensive Care. 2018;8(1):66

Distributive Shock Phases

EBB PHASE

- Hyperdynamic shock
- Vasodilation
- Decreased systemic vascular resistance
- Increased capillary permeability
- Absolute or relative intravascular hypovolemia
- Decreased MAP

FLOW PHASE

- Initial stabilization
- Excess fluid mobilization
- Metabolic turnover increased
- Innate immunity activated
- Hepatic acute-phase response
- Increased oxygen consumption
- Energy expenditure

Sources: *Ann Intensive Care*. 2018;8(1):66
Vet Clin North Am Small Anim Pract. 1980;10(3):523-532

Use the ROSE Model to Answer Four Key Questions

1. When to start intravenous fluids ?
2. When to stop intravenous fluids ?
3. When to start de-resuscitation ?
4. When to stop de-resuscitation ?

Source: *Ann Intensive Care*. 2018;8(1):66

① When to start intravenous fluids ?

Resuscitation

Life-threatening phase of severe circulatory shock

Occurs within minutes → Strong vasodilation

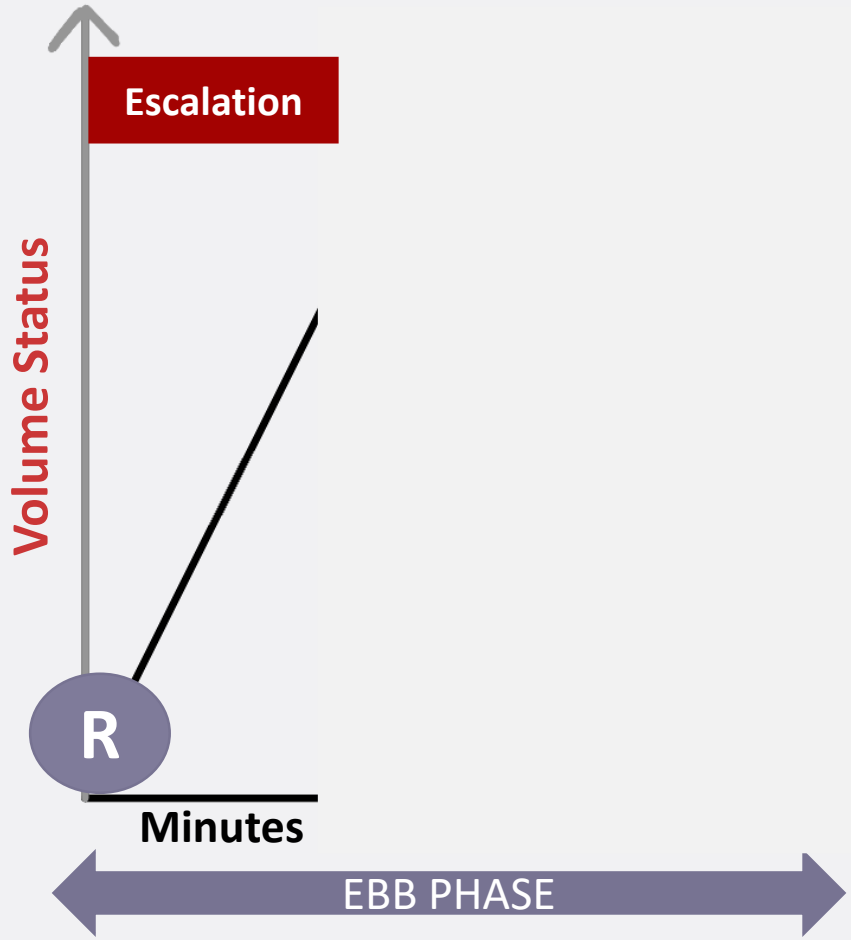
↓

Low MAP and microcirculatory impairment

First 3-6 hours → fluid resuscitation of ~30 mL/kg bolus

↓

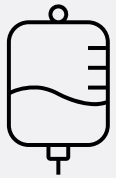
- Adopted by SSC Guidelines
- Based on observational data



Source: *Ann Intensive Care*. 2018;8(1):66
Pharmacotherapy. 2023;43(11):1182-1193

Aim of Fluid-Resuscitation

Restore intravascular volume



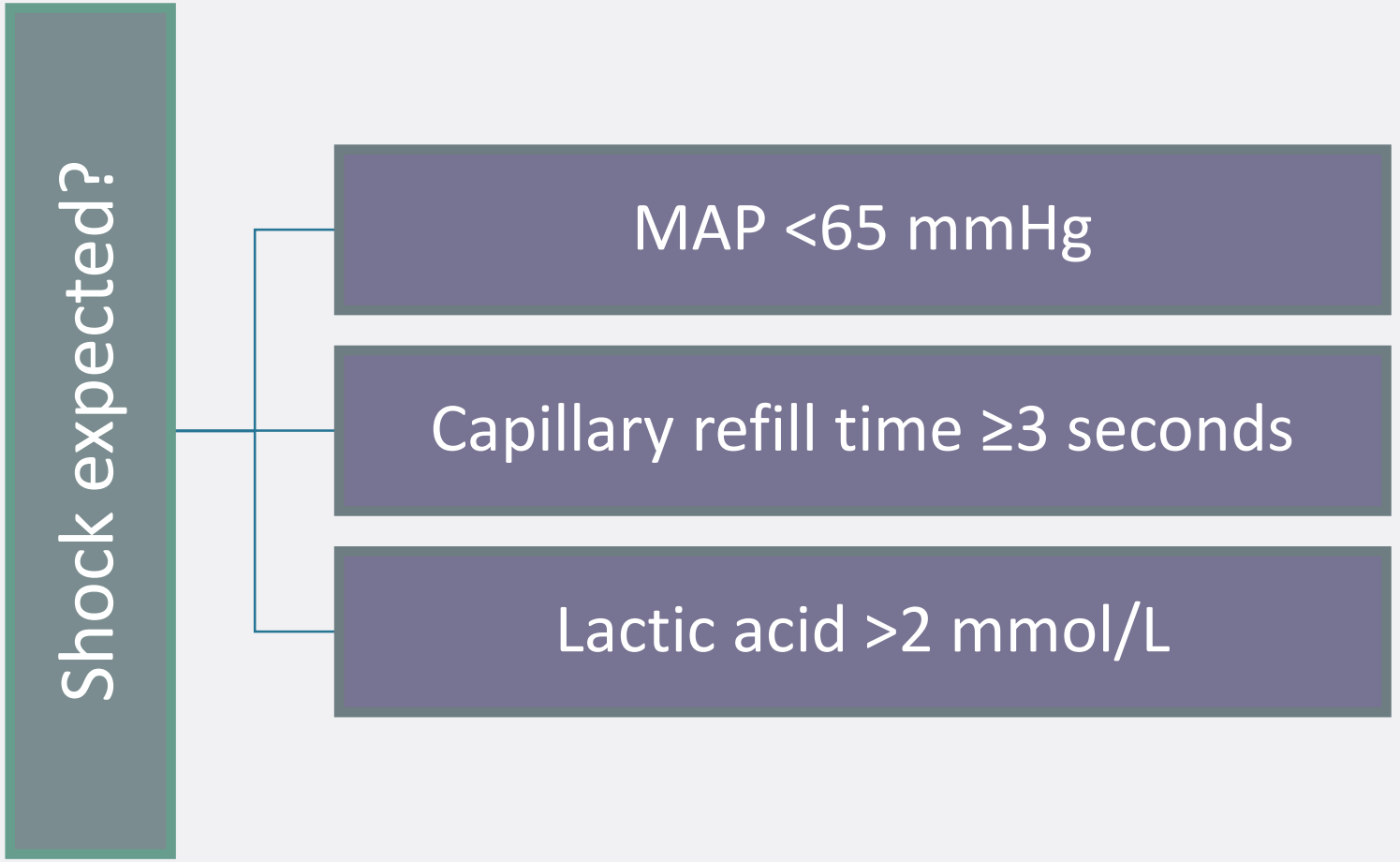
Increase CO

Augment oxygen delivery

Improve tissue oxygenation

Source: *Ann Intensive Care*. 2018;8(1):66

Signs to Resuscitate



Sources: *Intensive Care Med* (2022) 48:1781-1786
JAMA. 2023;329(22):1967-1980

Predicting Likelihood of Fluid Response

Marker	Definition	Normal Range	Change that indicates increased CO
CVP	Estimates right atrial pressure and cardiac preload	5-10 cm H_2O	-
PPV	Indicates change in pulse pressure during respiration with mechanical ventilation	10%-15%	>10-12%
End-expiratory occlusion test	Indicates an approximate 15 second occlusion of the endotracheal tube in intubated patient at end of expiration	Variable	Pulse pressure change >5%
Mini fluid challenge	Dynamic maneuver in which ~100 mL fluid given over 1 minute to predict responsiveness	Variable	Change in velocity time index >10%
PLR	Dynamic maneuver to assess changes in preload and output in response to leg raising	Variable	Change in SV >9% and pulse pressure >10%

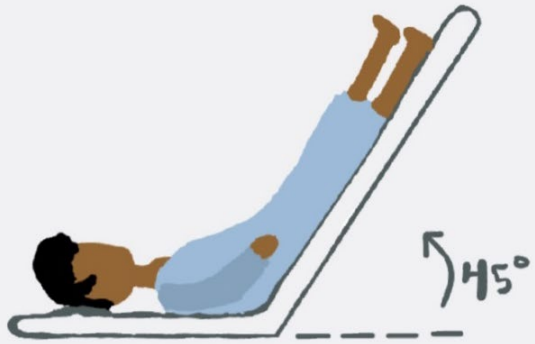
Sources: *JAMA*. 2023;329(22):1967-1980
Ann Intensive Care. 2018;8(1):66
J Gen Intern Med. 2019;34(9):1874-1883

PLR Test

Predicts fluid responsiveness

Approximates an “auto-bolus”

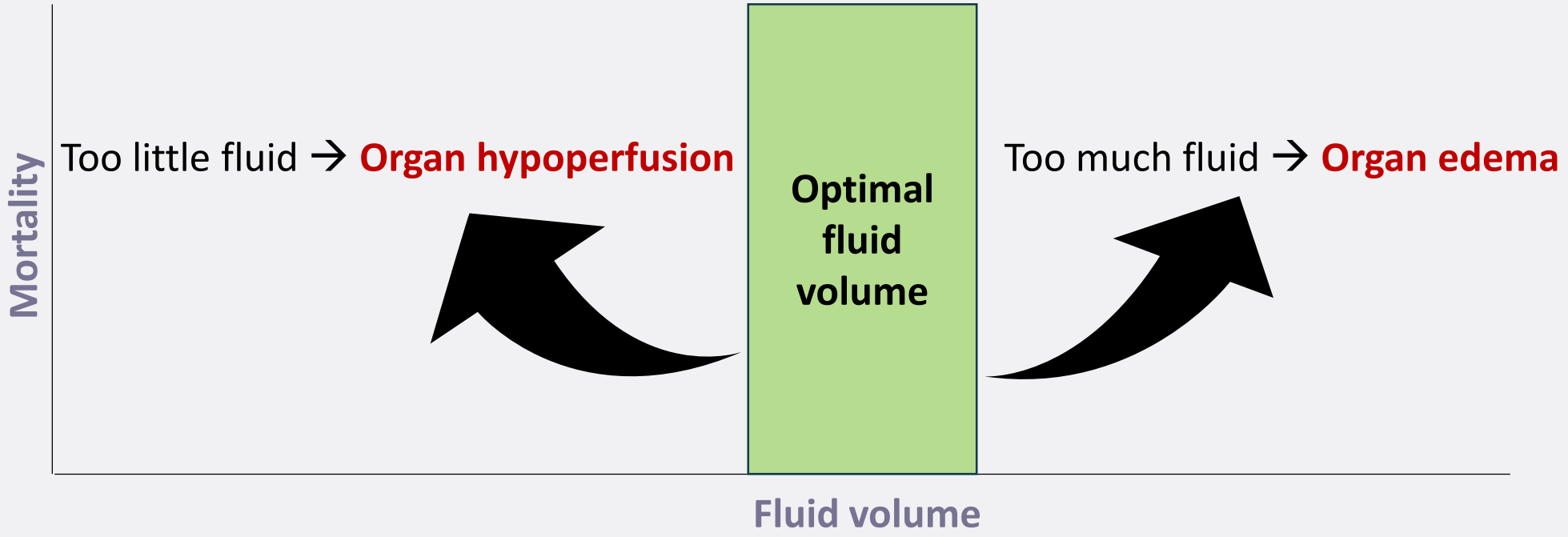
Threshold = 10% increase in SV and/or CO



Source: *Intensive Care Med*. 2020;35(10):1123-1128
JAMA. 2016;316(12):1298-1309.

Clinical Trials on Resuscitation

- Problem: they use one size fits all approach
- Important to individualize the need and amount of fluids
- Everyone responds differently



Source: Springer International Publishing; 2024:295-314

Rivers, et al.

Single center, parallel-group, randomized, controlled trial in emergency room patients with sepsis randomized

Question Among patients with septic shock, what is the efficacy of EGDT in decreasing mortality?

EGDT (n=130)

Giving fluids to obtain certain parameters with continuous monitoring

→ CVP 8-12mmHg
MAP >65mmHg
ScvO2 >70%
UOP >0.5 mL/kg/hr

Usual care (n=133)

Discretion of provider from protocol for hemodynamic stability

→ CVP 8-12mmHg
MAP >65mmHg
UOP >0.5 mL/kg/hr

Source: *N Engl J Med*. 2001;345(19):1368-1377

Rivers, et al.

Mortality: 30.5% vs 46.5% (RR 0.58; 95 CI 0.38-0.87; (p=0.009)

28-day mortality: 33.3% vs. 49.2% (RR 0.58; 95% CI 0.39-0.87; p=0.01)

60-day mortality: 44.3% vs. 56.9% (RR 0.67; 95% CI 0.46-0.96; p=0.03)

Times, h	Volume, L	P value
0-6	4.9 vs 3.5	<0.001
7-72	8.6 vs 10.6	0.01
0-72	13.4 vs 13.4	0.73

Source: *N Engl J Med*. 2001;345(19):1368-1377

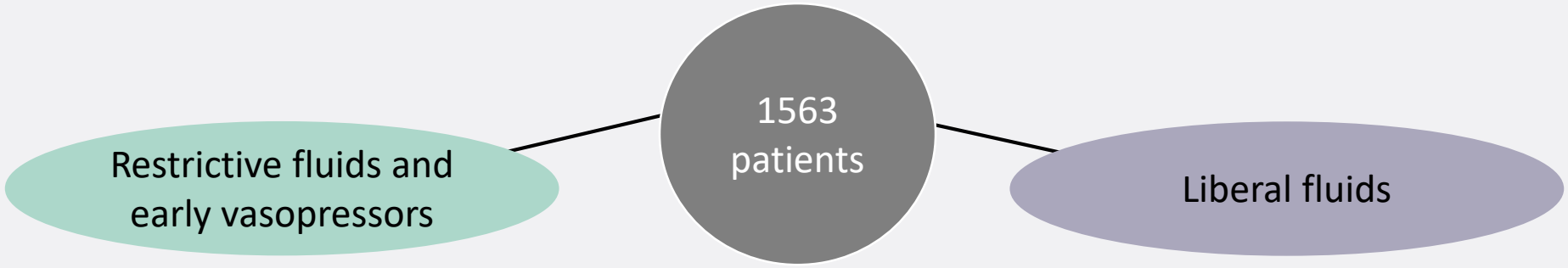
EGDT

Characteristics/Outcomes	RIVERS n=263	PROCESS n=1341	PROMISE n=1251	ARISE n=1591
IV Fluids Pre-Randomization, median	0	2.1	2	2.5
Lactate, mmol/L	>7	4-5	4	4
Afterload (vasopressor use), %	30	52-55	50	58
Time to ICU Admission, d	>6-8	<3	<2	<2
Immunomodulation (steroids), %	0	10	10	30
Mortality, %	30.5 vs 46.4	18.2 vs 21	29.2 vs 29.5	14.5 vs 15.7

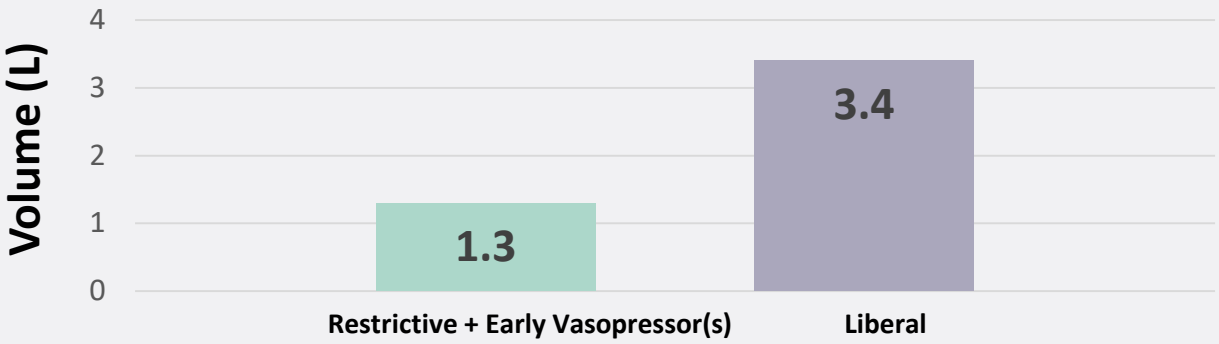
Sources: *N Engl J Med*. 2001;345(19):1368-1377
N Engl J Med. 2014;371(16):1496-1506
N Engl J Med. 2014;370(18):1683-1693
N Engl J Med. 2015;372(14):1301-1311

CLOVERS

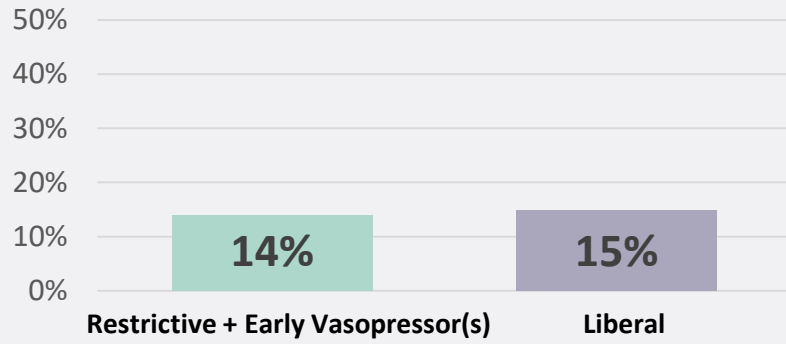
Does a restrictive fluid strategy during first 24 hours of resuscitation for sepsis-induced hypotension lead to a lower mortality before discharge by day 90 than a liberal strategy



Median fluid volume at 24 hours



90-day mortality



Source: *N Engl J Med*. 2023;388(6):499-510

Assessment Question 1

Which of the following is true when it comes to de-resuscitation?
(Pharmacists and Nurses)

A. It involves aggressive fluid administration
B. It aims to maintain a positive fluid balance
C. It aims to achieve a controlled removal of fluids
D. It is primarily focused on restoring blood pressure

Assessment Question 1

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② When to stop intravenous fluids ?

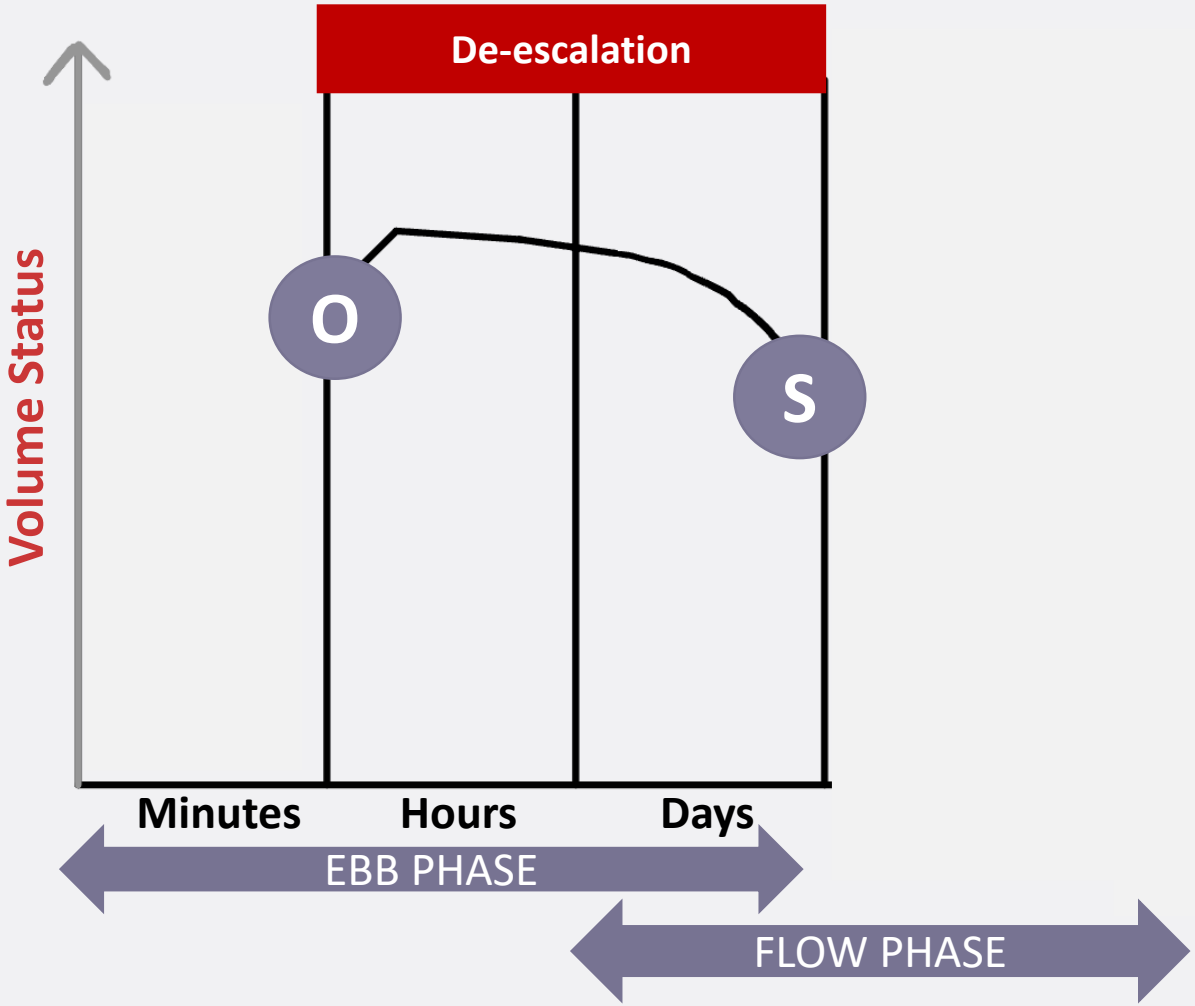
De-escalation: Optimization and Stabilization

Goal

Maintain perfusion and facilitate organ dysfunction resolution

Maintain perfusion to organs and tissues while avoiding fluid overload

Resolution of signs to resuscitate



Sources: *Intensive Care Med*. 2022;48(12):1781-1786
Ulus Cerrahi Derg. 2014;30(3):153-159
Ann Intensive Care. 2018;8(1):66

CLASSIC

Does restrictive IV fluid improve 90-day mortality in patients with septic shock compared to standard therapy?

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

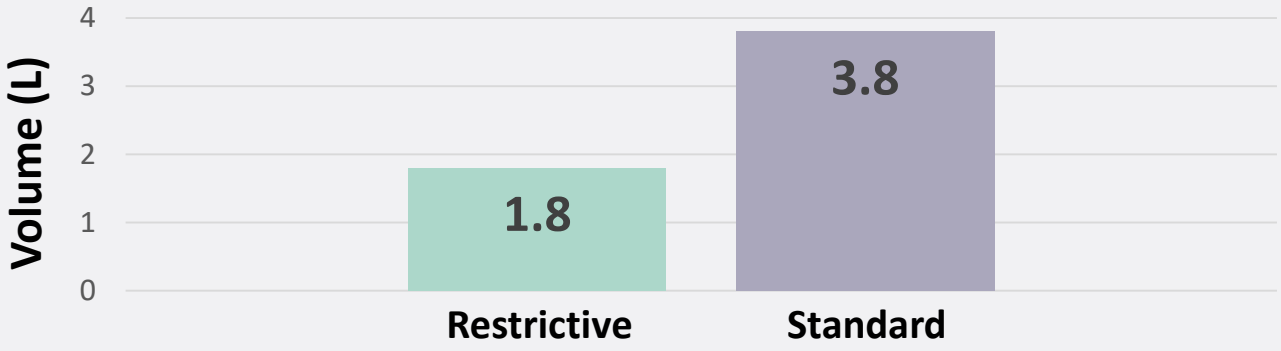
Restrictive Fluid

1554 patients 31 centers

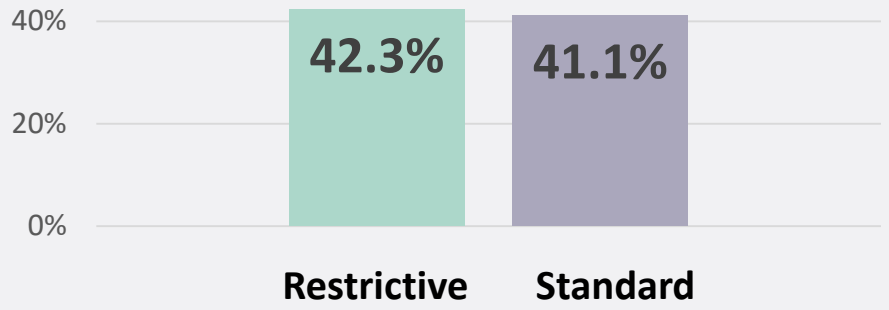
Standard Fluid

Fluids given at provider's discretion

Median volume administered after 90 days



90-day mortality



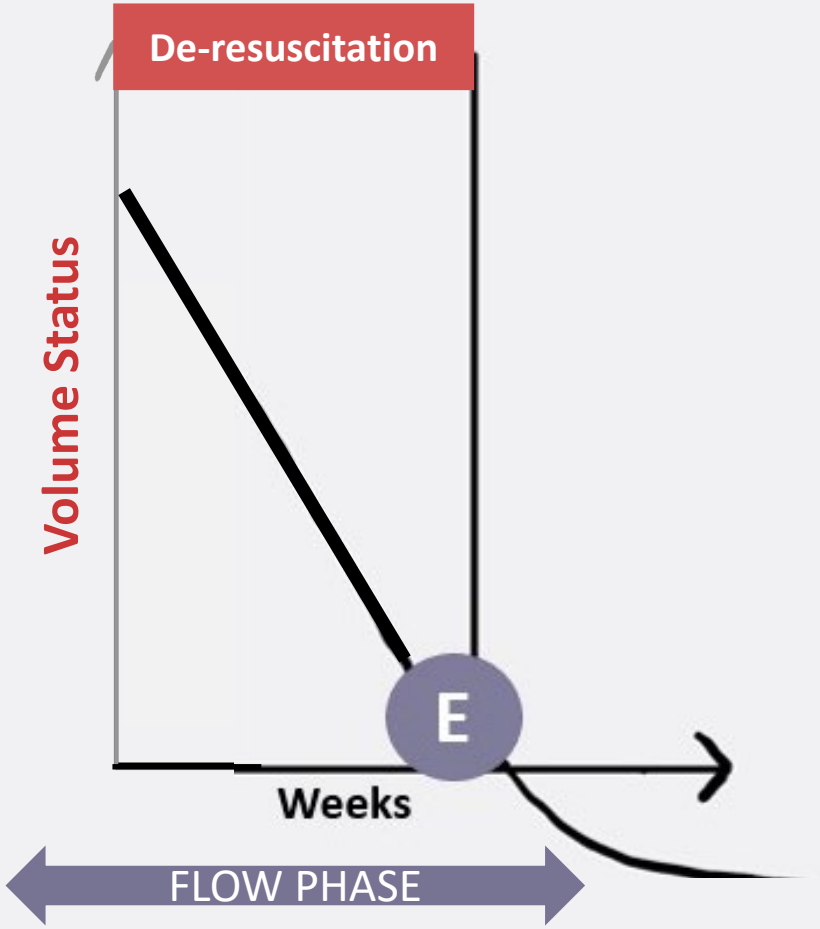
Source: *N Engl J Med*. 2022;386(26):2459-2470

③ When to start de-resuscitation ?

Evacuation

Goal

Treat and/or prevent end-organ damage resulting from fluid overload



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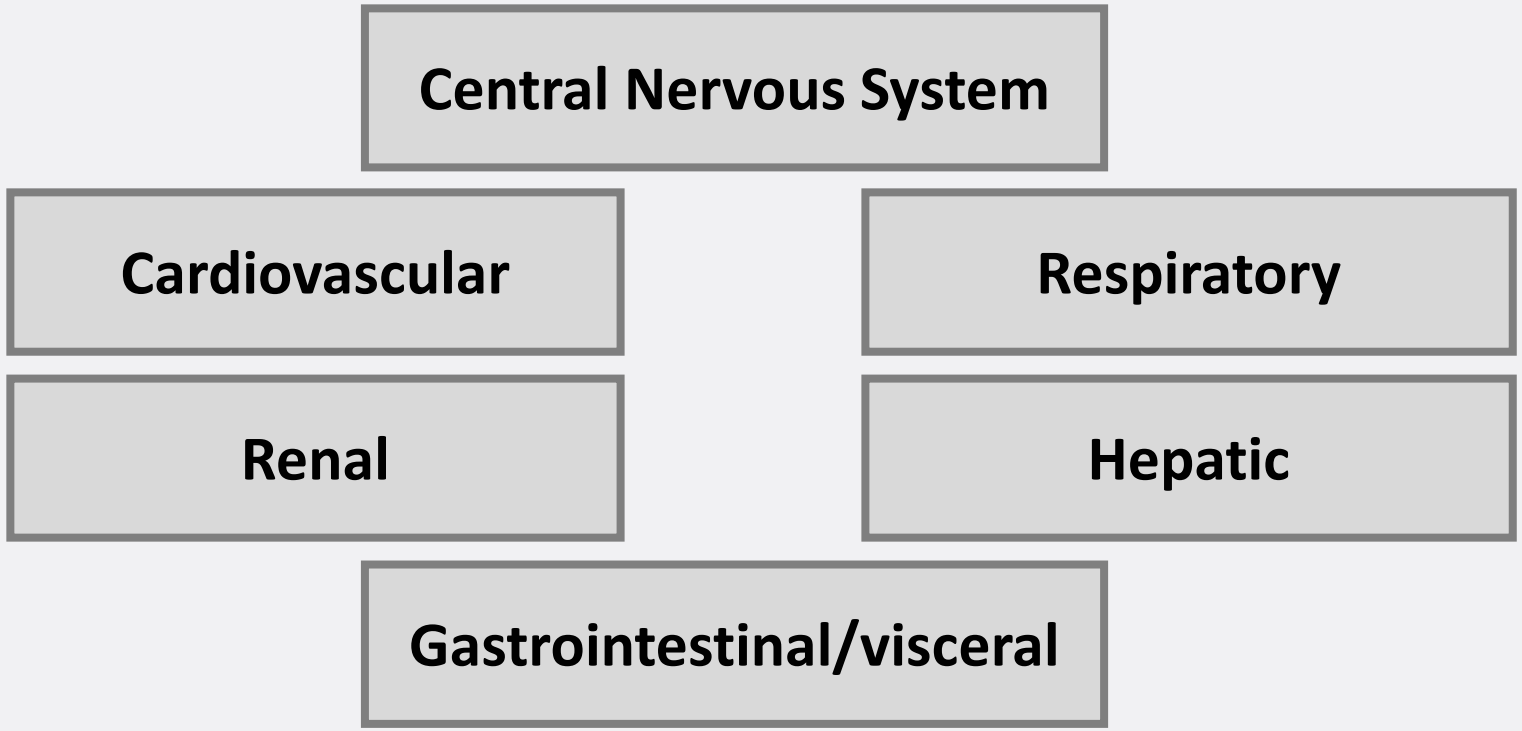
Anaesthesiol Intensive Ther. 2014;46(5):361-380

Signs to De-resuscitate



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Ann Intensive Care. 2018;8(1):66
Anaesthesiol Intensive Ther. 2014;46(5):361-380
JAMA. 2023;329(22):1967-1980

Evacuation – Estimating Fluid Accumulation

Daily documentation of

- Fluid intake
- Urine output
- CFB
- Weight

CFB → sum total of fluid accumulation over a period of time

Assessment Question 2

Volume overload in critically ill patients may result in which of the following? (All)

A. Increased hepatic congestion
B. Pulmonary edema
C. Kidney injury
D. B and C only
E. All of the above

Assessment Question 2

Volume overload in critically ill patients may result in which of the following? (All)

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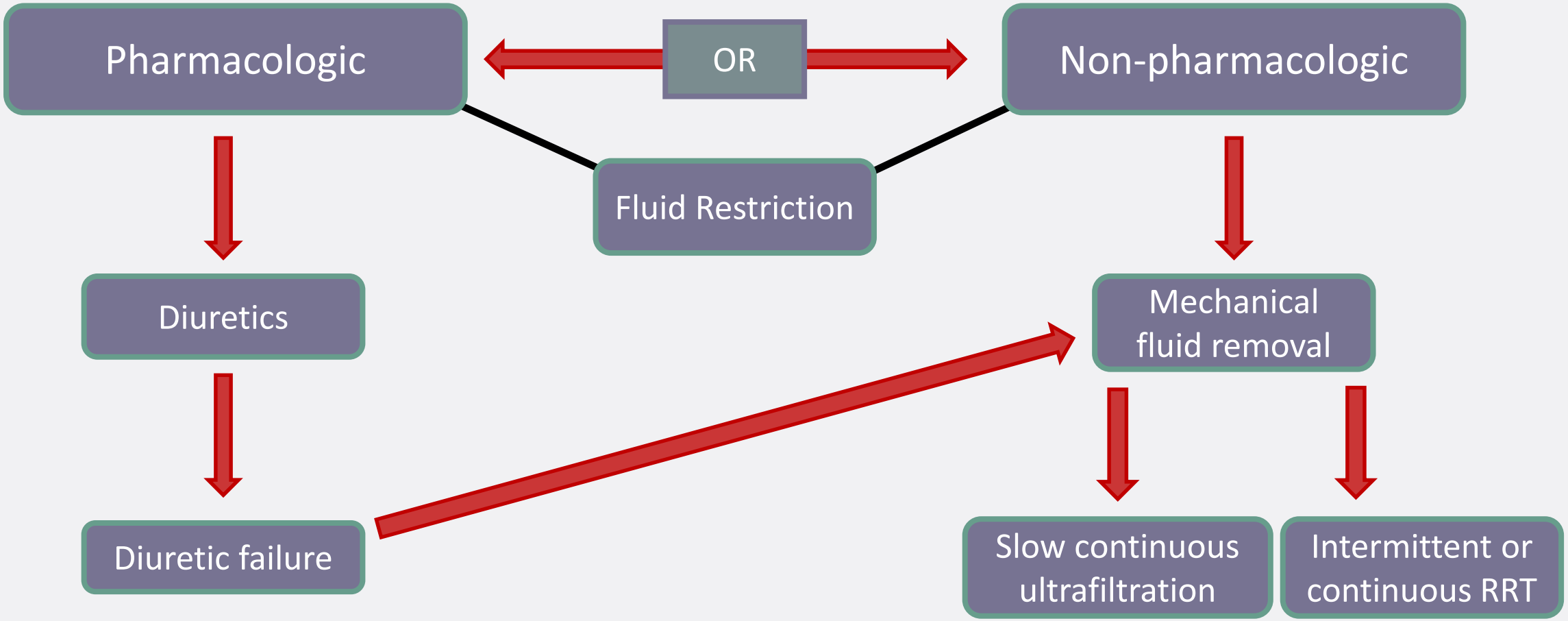
Measures to Remove Excess Fluid



Source: *Intensive Care Med*. 2022;48(12):1781-1786

Malbrain et al.

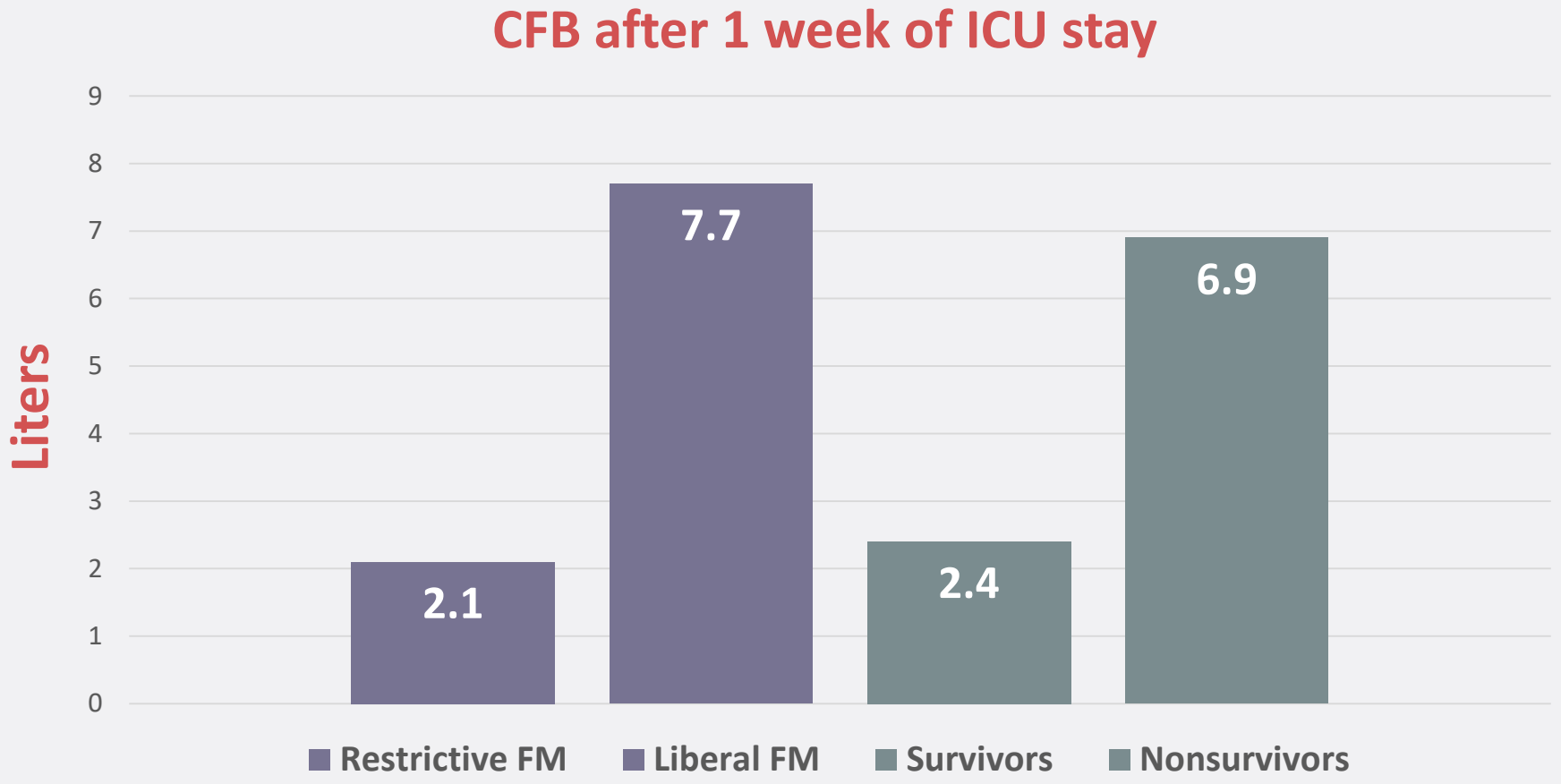
Investigated the effects of fluid removal with either furosemide or RRT with net ultrafiltration on IAP

19,902 patients studied
Intervention had to be a strategy or protocol attempting to obtain a neutral or negative balance

Do non-survivors have a more positive fluid balance?
Does outcome improve with an intervention to limit fluid intake or lower fluid balance?

Source: *Anaesthesiol Intensive Ther*. 2014;46(5):361-380

Malbrain et al.



Source: *Anaesthesiol Intensive Ther*. 2014;46(5):361-380

Malbrain et al.

Dose-related effect observed → the more negative the net fluid balance or fluid removal, the greater the decrease in IAP

Restrictive strategy → associated with lower mortality compared to liberal fluid management
24.7% vs 33.2%; OR 0.42 [95% CI 0.32, 0.55]; p <0.0001

Conclusion: Suggest a goal of a zero or negative fluid balance by day 3 and to keep the CFB on day 7 as low as possible

Source: *Anaesthesiol Intensive Ther*. 2014;46(5):361-380

RADAR-2

Objective

Investigate the feasibility, safety, and clinical outcomes of a strategy of conservative fluid administration compared with usual care in critically ill adults

Design

Open-label, parallel-group, allocation concealed randomized pilot trial

Population

180 intubated critically ill patients (40% sepsis)

Intervention

2-stage fluid strategy and de-resuscitation vs usual care on ICU days 2-5

1. De-escalation: discontinuation of maintenance fluids
2. De-resuscitation: furosemide + spironolactone for goal net -1 to 3L

Net fluid balance > +2L or clinical edema AND

Norepinephrine <0.2 mcg/kg/min, lactate <3.5

Source: *Intensive Care Med*. 2022;48(2):190-200

RADAR-2

Outcome	Intervention (n=88)	Usual care (n=88)	P value
Balance day 2-3, L	-0.84 (1.8)	+0.13 (1.4)	<0.01
CFB at Day 3, L	+2 (3.3)	+2.9 (3.5)	0.04
CFB at day 5, L	+0.39 (4.2)	+3.7 (4.4)	<0.01
CFB at ICU discharge, L	-0.46 (6.5)	+1.2 (6.6)	0.07
Death within 28 days, n (%)	19 (21.4)	14 (15.6)	0.45
Death within 180 days, n (%)	25 (28.4)	21 (23.9)	0.61
Data expressed as mean (SD) or number (%)			

Source: *Intensive Care Med*. 2022;48(2):190-200

IRIHS

Objective

Assess the efficacy and safety of a diuretic strategy to overcome positive fluid balance in patients on invasive mechanical ventilation after hemodynamic stabilization

Design

Multicenter, single-blind, randomized, controlled trial

Population (n=166)

77 → furosemide	89 → control
• Once or twice daily until extubated • Dose adapted by the physician with aim to reach the reference weight → maximum dose 250 mg	Diuretics prohibited unless for rescue

Primary Outcome

Weight variation from reference weight to successful extubation

Source: *Crit Care*. 2021;25(1):98

IRIHS

Baseline Characteristics	Control (n=89)	Diuretics (n=77)
Weight at randomization, kg	84 [75, 97]	88.5 [73, 99]
CKD, n(%)	3 (3.4)	1 (1.3)
Admission		
Acute respiratory failure	42 (47.2)	33 (42.9)
Sepsis/septic shock	28 (31.4)	21 (27.2)
Hemorrhagic shock	5 (5.6)	4 (5.2)

Data expressed as number (%) or median [Q1-Q3]

Source: *Crit Care*. 2021;25(1):98

IRIHS

Primary outcome	Control (n=89)	Intervention (n=77)	Mean difference 95% CI	P value
Primary analysis, kg	-	-	-4.8 CI 95% [-7.3 to -2.5]	<0.001
Complete cases, kg **n=144**	6.4 [5, 11.2]	1.4 [1, 4.5]	-5.1 [-7.4; -2.8]	<0.001
Data expressed as number (%) or median [IQR]				

Conclusion:

- Protocolized diuretic therapy reduced accumulation in patients receiving mechanical ventilation without major adverse effects

Source: *Crit Care*. 2021;25(1):98

Bissell et al.

Impact of protocolized diuresis for de-resuscitation in the MICU

Pre and post single-center pilot study in the MICU

Mechanical ventilation with either:
- Clinical signs of volume overload on chest radiograph or exam
- Positive fluid balance since admission eligible

Historical control (n=273)

Diuresis per clinician discretion for a 2-year period

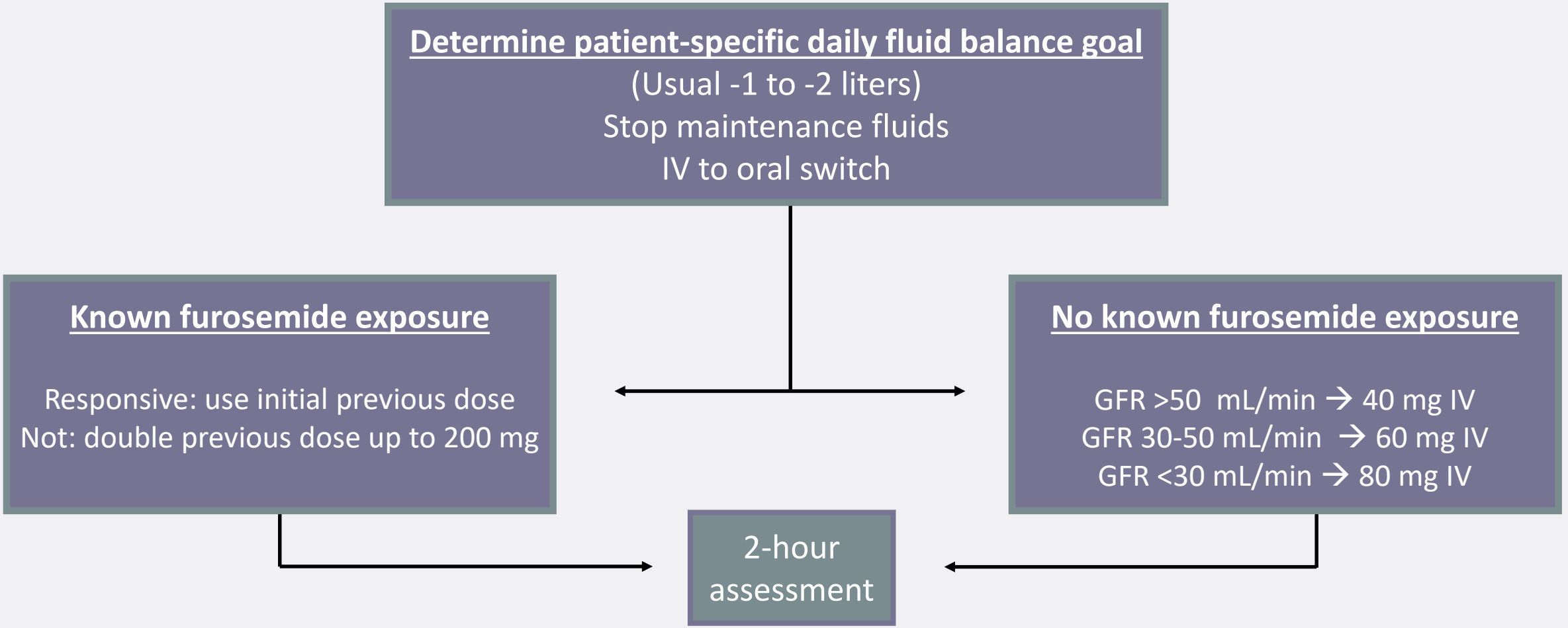
Post-protocol group (n=91)

Diuresis protocol for 1 year

80 [40-200] ← Total cumulative dose, mg *expressed as median [IQR] → 240 [120-420]

Source: *Crit Care*. 2020;24(1):70

Bissell et al.



Source: *Crit Care*. 2020;24(1):70

Bissell et al.

Outcomes	Historical cohort (n=273)	Intervention cohort (n=91)	P value
72h fluid balance, L	0.27 (-2.3-3)	-2257 (-5.7-0.9)	<0.0001
Ventilator free days	8 (5–13)	5 (5–12)	0.441
ICU free days	17 (7–21)	19 (13–22)	0.03
In-hospital mortality	44 (16.1)	5 (5.5)	0.008
RRT receipt in ICU	17 (6.2)	0	<0.0001
Hypokalemia	0	3 (3.3)	0.015
Hypernatremia	19 (6.9)	19 (20.9)	0.001

Data expressed as mean (SD), median (IQR), and number (%)

Conclusion:

- Significant decrease in net CFB at 72 hours following shock resolution
- Potential benefit on clinical outcomes including mortality and ICU LOS

Source: *Crit Care*. 2020;24(1):70

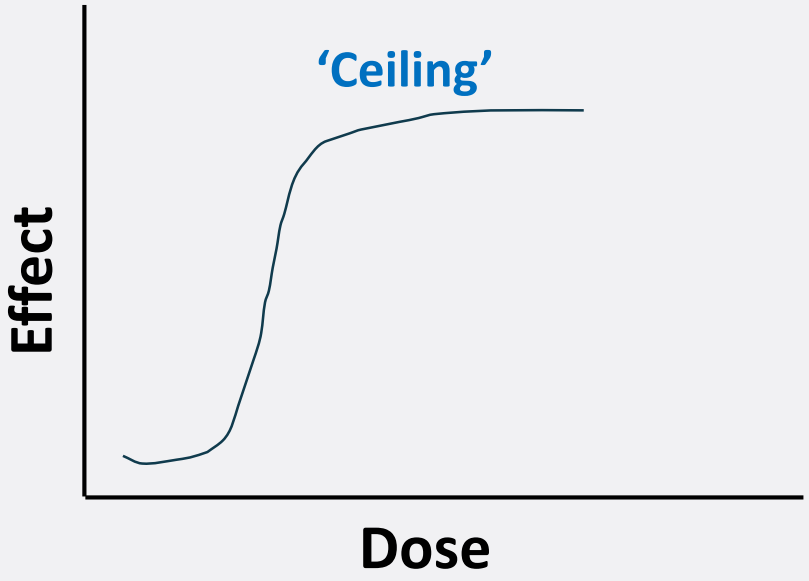
Diuretic Options

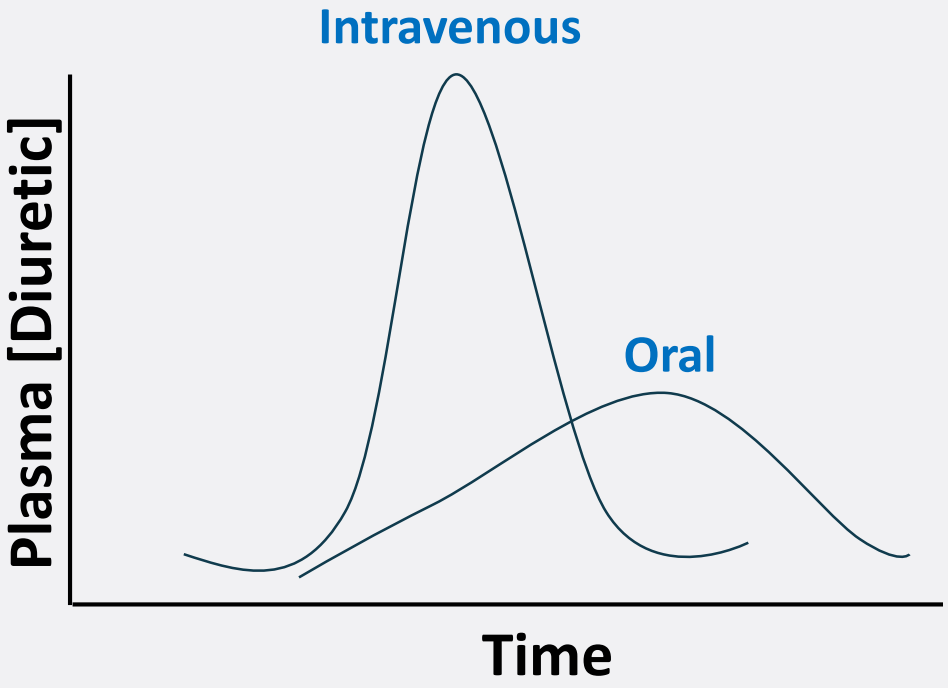
Electrolyte Effects	Na^+	K^+ & Mg^{2+}	HCO^{3-}
Loop diuretic	↑↓	↓	↑
Carbonic Anhydrase Inhibitors	-	↓	↓
Thiazide	↓↓	↓	↑
Potassium sparing	-	↑	↓

Furosemide	Bumetanide	Metolazone	Chlorothiazide	Indapamide	Acetazolamide	Spironolactone
20-160 mg/dose IV	0.5-3 mg IV Q6H	5-10 mg PO daily	500-1000 mg IV Q12-24H	2.5-5 mg PO daily	500 mg IV Q12H	25-50 mg PO TID

Sources: *Ann Intensive Care*. 2020;10(1):64
Intensive Care Med. 2022;48(12):1781-1786
N Engl J Med. 2011 Mar 3;364(9):797-805
Acta Anaesthesiol Scand. 2018;62(7):936-944
Lexi-Drugs

Loop Diuretic Activity





Source: *Clin J Am Soc Nephrol*. 2019;14(8):1248-1257

Assessment Question 3

Which of the following would warrant de-resuscitation? (Pharmacists and Nurses)

A. Lactate change from 6 mmol/L to 4 mmol/L in a patient with septic shock after IV fluid bolus
B. Patient with heart failure that develops shortness of breath and elevated BNP
C. Hypotensive patient with septic shock (lactate 4 mmol/L) and blood pressure responds after PLR test
D. A normal IAP and a positive PLR test

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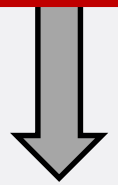
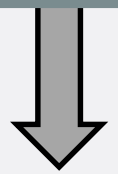
Storage and Preparation

Bumetanide and furosemide continuous infusion



Beyond use date: 24 hours at room temperature



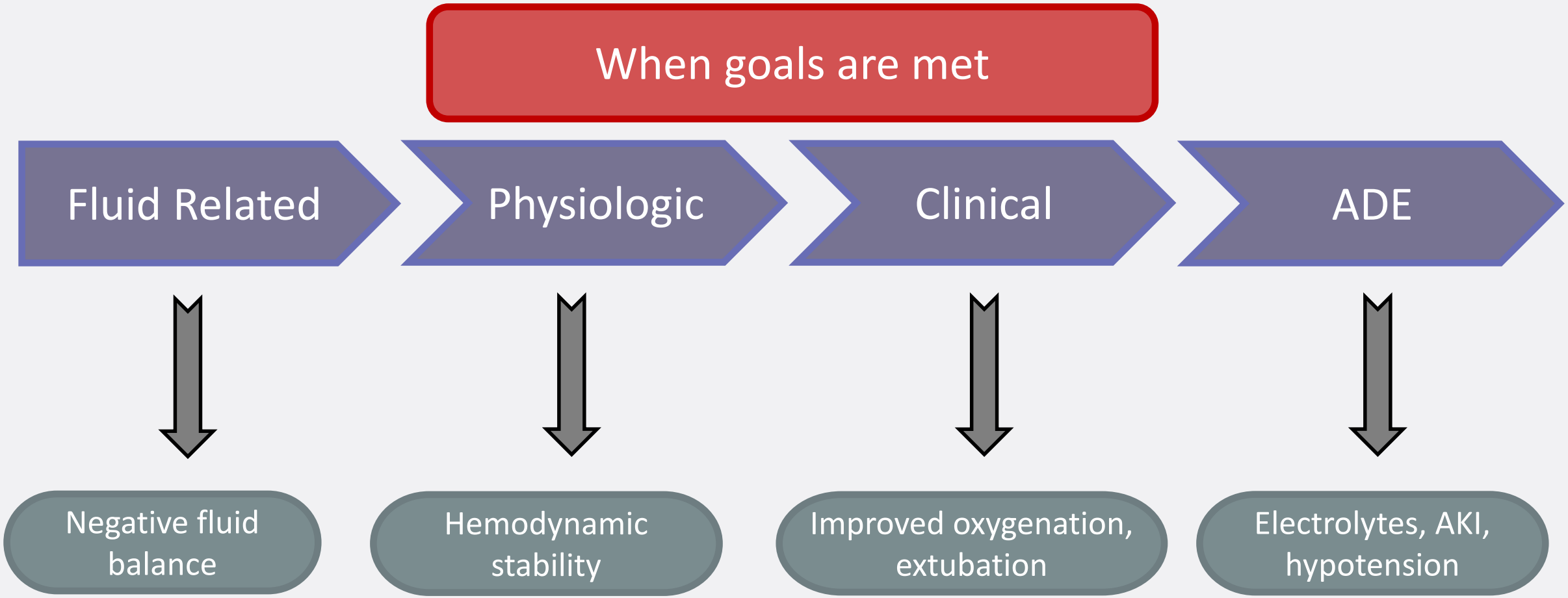
Protect from light

Sources: USP 797

4

When to stop de-resuscitation ?

When to Stop De-resuscitation?



Sources: *Intensive Care Med*. 2022;48(12):1781-1786
Ulus Cerrahi Derg. 2014;30(3):153-159
Ann Intensive Care. 2018;8(1):66

Implementation of Fluid Stewardship in a MICU

Fluid stewardship services integrated into adult MICU at a large community hospital

Data reported and categorized based on → 4 Rights, ROSE

305 patients reviewed → 2597 pharmacists made recommendations

4 Rights	Interventions, n (%)
Right patient	194 (39)
Right route	165 (33)
Right drug	85 (17)
Right dose	55 (11)

ROSE	Interventions, n (%)
Resuscitation	6 (1)
Optimization	18 (3)
Stabilization	392 (79)
Evacuation	83 (17)

Source: *Am J Health Syst Pharm*. 2022;79(12):984-992

Assessment Question 4

Which of the following is the optimal storage location for the discussed medications used for fluid de-resuscitation? (Pharmacy Technicians)

A. Refrigerator
B. Room temperature
C. Freezer
D. Any of the above

Assessment Question 4

Which of the following is the optimal storage location for the discussed medications used for fluid de-resuscitation? (Pharmacy Technicians)

A. Refrigerator
B. Room temperature
C. Freezer
D. Any of the above

Assessment Question 5

Which of the following medications are commonly used initially for fluid de-resuscitation in critically ill patients? (Pharmacy Technicians)

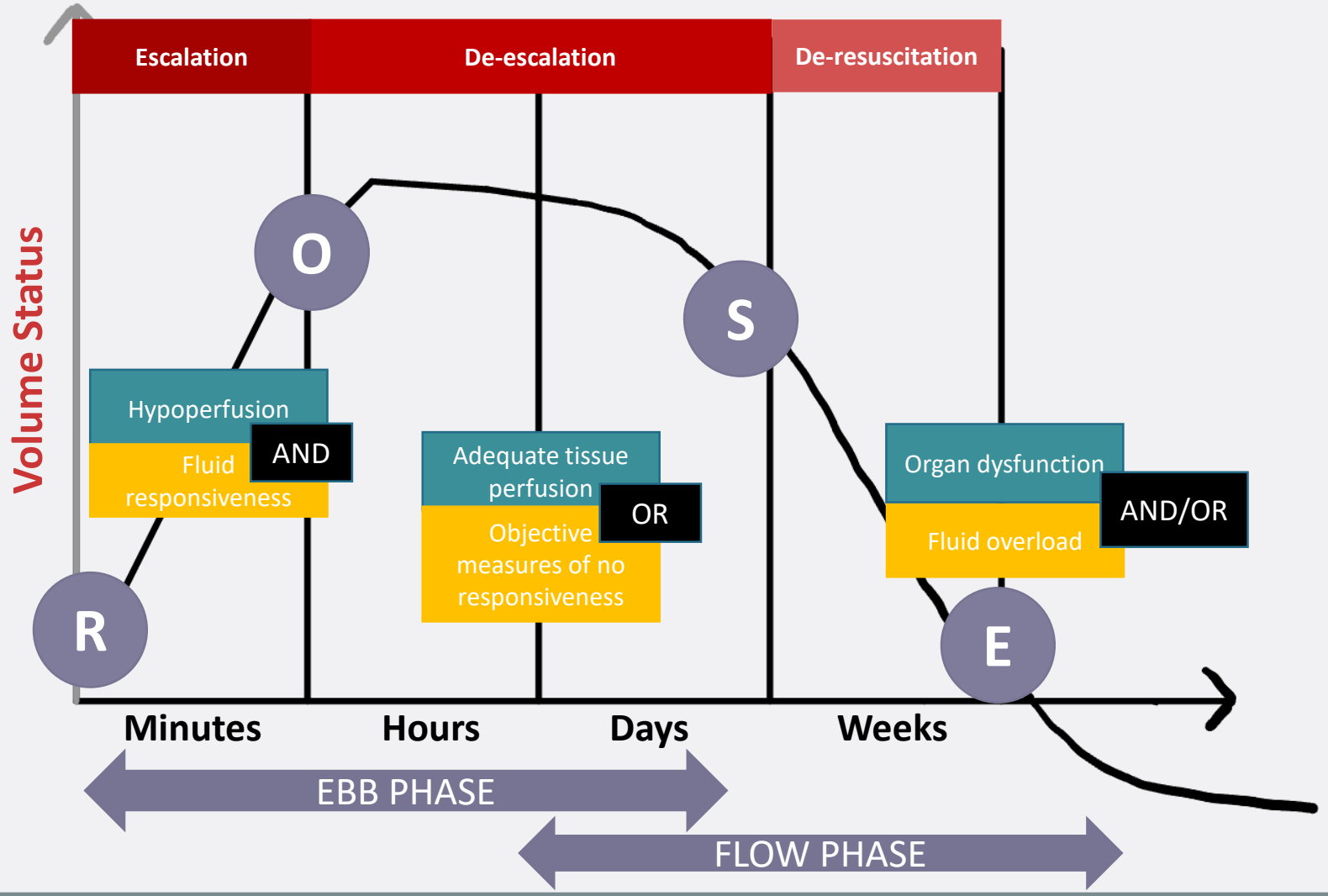
A. Epinephrine
B. Furosemide
C. Spironolactone
D. Mannitol

Assessment Question 5

Which of the following medications are commonly used initially for fluid de-resuscitation in critically ill patients? (Pharmacy Technicians)

A. Epinephrine
B. Furosemide
C. Spironolactone
D. Mannitol

ROSE Model



Sources: *Intensive Care Med*. 2022;48(12):1781-1786
Ulus Cerrahi Derg. 2014;30(3):153-159
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