Fluid management and AKI

Farin Rashid Farokhi
Associate Professor of Nephrology
Shahid Beheshti University of Medical Science
Masih Daneshvari Hospital

Case presentation

A 72-year-man was admitted to an emergency room with pneumonia, sepsis and hypotension. There was a previous history of DM, COPD, CKD, and IHD. He received 2.5 liters of normal saline and broad spectrum antibiotics in the emergency department. Mechanical ventilation was started because of severe hypoxia and confusion. Several hours later, he was transferred to the ICU. The body weight was 75 kg. The ICU findings included the followings:

- T: 39° C, HR:110, BP: 80/50 mmHg
- Physical exam: 2+ peripheral edema
- CVP:14 mmHg
- Mechanical Ventilation Mode: SIMV (Intermittent spontaneous breathing)
- O2 saturation: 97%
- Cr: 1.7 mg/dL
- Tidal volume: 400 mL
- ECG: Frequent PVC (No finding in favour of acute ischemia)
- Cardiac Ejection Fraction: 40%
- WBC: 20,000
- Lactate: 6.2 mmol/L

Case presentation

A 72-year-man was admitted to an emergency room with pneumonia, sepsis and hypotension. There was a previous history of DM, COPD, CKD, and IHD. He received 2.5 liters of normal saline and broad spectrum antibiotics in the emergency department. Mechanical ventilation was started because of severe hypoxia and confusion. Several hours later, he was transferred to the ICU. The body weight was 75 kg. The ICU findings included the followings:

- T: 39° C, HR:110, BP: 80/50 mmHg
- Physical exam: 2+ peripheral edema
- CVP:14 mmHg
- Mechanical Ventilation Mode: SIMV (Intermittent spontaneous breathing)
- O2 saturation: 97%
- Cr: 1.7 mg/dL
- Tidal volume: 400 mL
- ECG: Frequent PVC (No finding in favour of acute ischemia)
- Cardiac Ejection Fraction: 40%
- WBC: 20,000
- Lactate: 6.2 mmol/L

Administration of More fluids may be risky.
Administration of more fluids may be beneficial.

The reasons for peripheral edema in critically ill patients

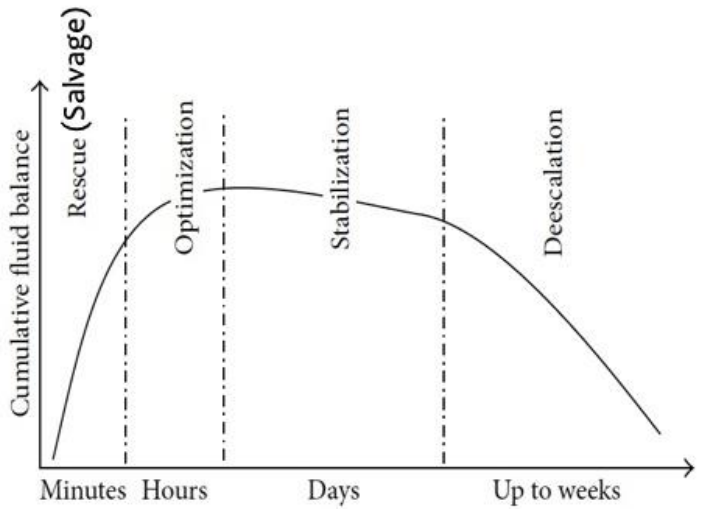
- Right and left ventricular failure
- Impaired lymphatic drainage due to decreased muscular activity
- Decreased oncotic pressure resulted from receiving large volume of intravenous fluids
- Sodium retention by the kidneys due to hypo-perfusion
- Ventilator induced positive fluid balance
- Fluid leak as a result of endothelial dysfunction

CVP can change with the following factors:

- Intravascular volume
- Patient's posture
- Right ventricular compliance
- Isolated left sided heart disease
- Valvular heart diseases
- Pulmonary vascular disease
- Changes in intra-thorasic pressure
- Tense ascites
- Peripheral venous tones

Phases of fluid resuscitation (The ROSE model)

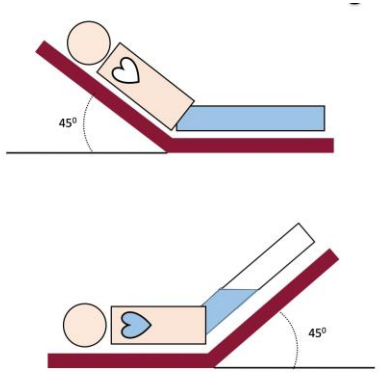
	Rescue	Optimization	Stabilization	De-escalation
Goals	Life-saving	Organ rescue	Organ Support	Organ Recovery
Phenotype	Severe Shock	Unstable	Stable	Recovering
Fluid Therapy	Fluid Boluses	Fluid challenges	Neutral balance	Fluid removal

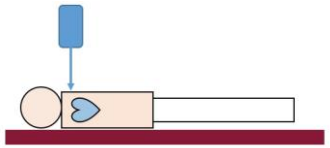


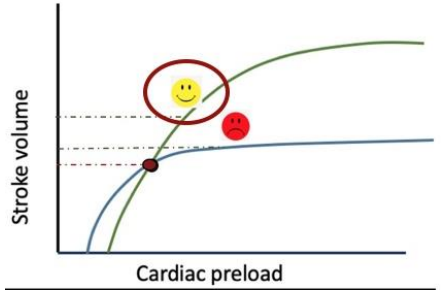
Hoste E.A., et al. British Journal Anaesthesia 2014

Back to patient

- Age: 72 year, sex: male, weight: 75 kg
- Previous history of DM, COPD, CKD, and IHD
- Admission with pneumonia, sepsis, hypotension, fever, and tachycardia
- Receiving of 2.5 liters of normal saline and broad spectrum antibiotics in the emergency department
- Starting Mechanical ventilation, and transferring to the ICU
- An ejection fraction of 40% and Peripheral edema in the ICU examinations
- Leukocytosis, High lactate, and a serum Cr of 1.7 mg/dL in the laboratory findings achieved on the first day of ICU admission







- Inotrope and vasopressor medications were started.
- Fluid challenge test led to a 10% increase in the stroke volume.
- The patient received more fluids.

Case presentation (continuation)

The doses of vasopressor and inotrope medications were reduced within 24 hours to keep MAP> 65 mmHg. The patient was weaned from the mechanical ventilation after 48 hours, and oral nutrition was started. The intravenous volume was 2.5 L of normal saline per day. By the development of dyspnea on the second day, the oxygen flow increased to 6 L/min. At the time of nephrology consultation on the third day of ICU admission, his urine output had been decreased to 300 mL for the previous 12 hours. Chest-x-ray revealed diffuse bilateral infiltration. Other findings included the followings:

- BP: 100/70 (dependent to vasopressors/inotropes)
- Peripheral edema: +3
- Cumulative fluid balance: +8 lit
- Hgb: 10.3 g/dL, HCT: 30%
- BUN: 120 mg/dL
- Creatinine: 3.5 mg/dL
- Na:136 mEq/L
- K: 4.8 mEq/L
- CL: 110 mEq/L
- PH: 7.08, HCO3: 10 mEq/L

Probable risk factors for the development of AKI

- Age: 72 year, sex: male, weight: 75 kg
- Previous history of DM, COPD, CKD, and IHD
- Admission with pneumonia, sepsis, hypotension, fever, and tachycardia
- Receiving of 2.5 liters of normal saline? and broad spectrum antibiotics in the emergency department
- Starting Mechanical ventilation, and transferring to the ICU
- An ejection fraction of 40% and Peripheral edema in the ICU examinations
- Leukocytosis, High lactate, and a serum Cr of 1.7 mg/dL in the ICU laboratory findings

Case presentation (continuation)

The doses of vasopressor and inotrope medications were reduced within 24 hours to keep MAP> 65 mmHg. The patient was weaned from the mechanical ventilation after 48 hours, and oral nutrition was started. The intravenous volume was 2.5 L of normal saline per day. By the development of dyspnea on the second day, the oxygen flow increased to 6 L/min. At the time of nephrology consultation on the third day of ICU admission, his urine output had been decreased to 300 mL for the previous 12 hours. Chest-x-ray revealed diffuse bilateral infiltration. Other findings included the followings:

- BP: 100/70 (dependent to vasopressors/inotropes)
- Peripheral edema: +3
- Cumulative fluid balance: +8 lit
- Hgb: 10.3 g/dL, HCT: 30%
- BUN: 120 mg/dL
- Creatinine: 3.5 mg/dL
- Na:136 mEq/L
- K: 4.8 mEq/L
- CL: 110 mEq/L
- PH: 7.08, HCO3: 10 mEq/L

- Current SCr to Baseline SCr: 3.5/1.7= 2.05
- Urine output: 300/12= 33 mL/h or 0.33 mL/kg/h

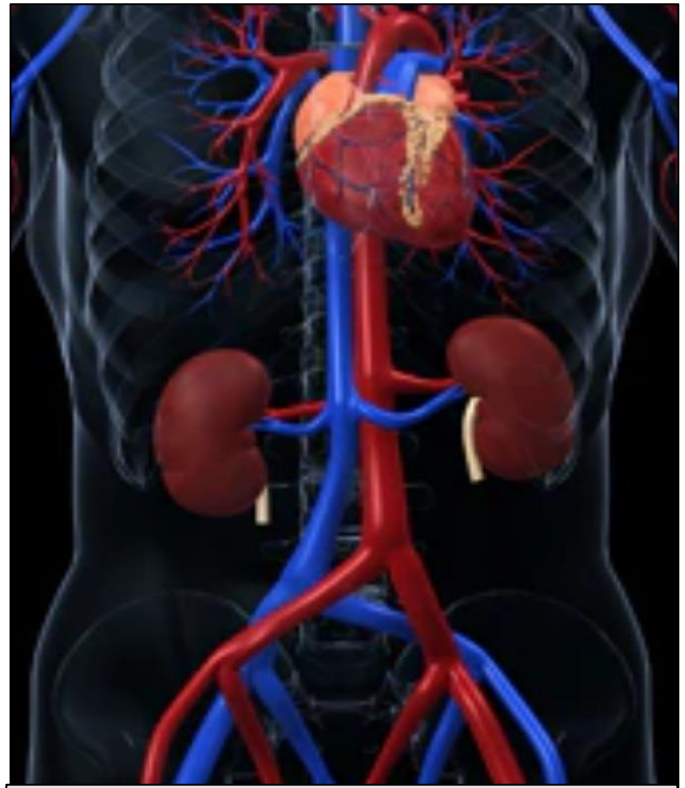
Definition of AKI based on KDIGO criteria

stage	Serum Creatinine (SCr)	Urine Outcome
1	1.5 to 1.9 times baseline or ≥ 0.3 mg/dL increase in SCr within 48 hours	< 0.5 mL/kg/h for 6-12 hours
2	2 to 2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 hours
3	3 times baseline or Increase in SCr ≥ 4mg/dL or Initiation of RRT	< 0.3 mL/kg/h for ≥ 24 hours or Anuria for ≥ 12 hours

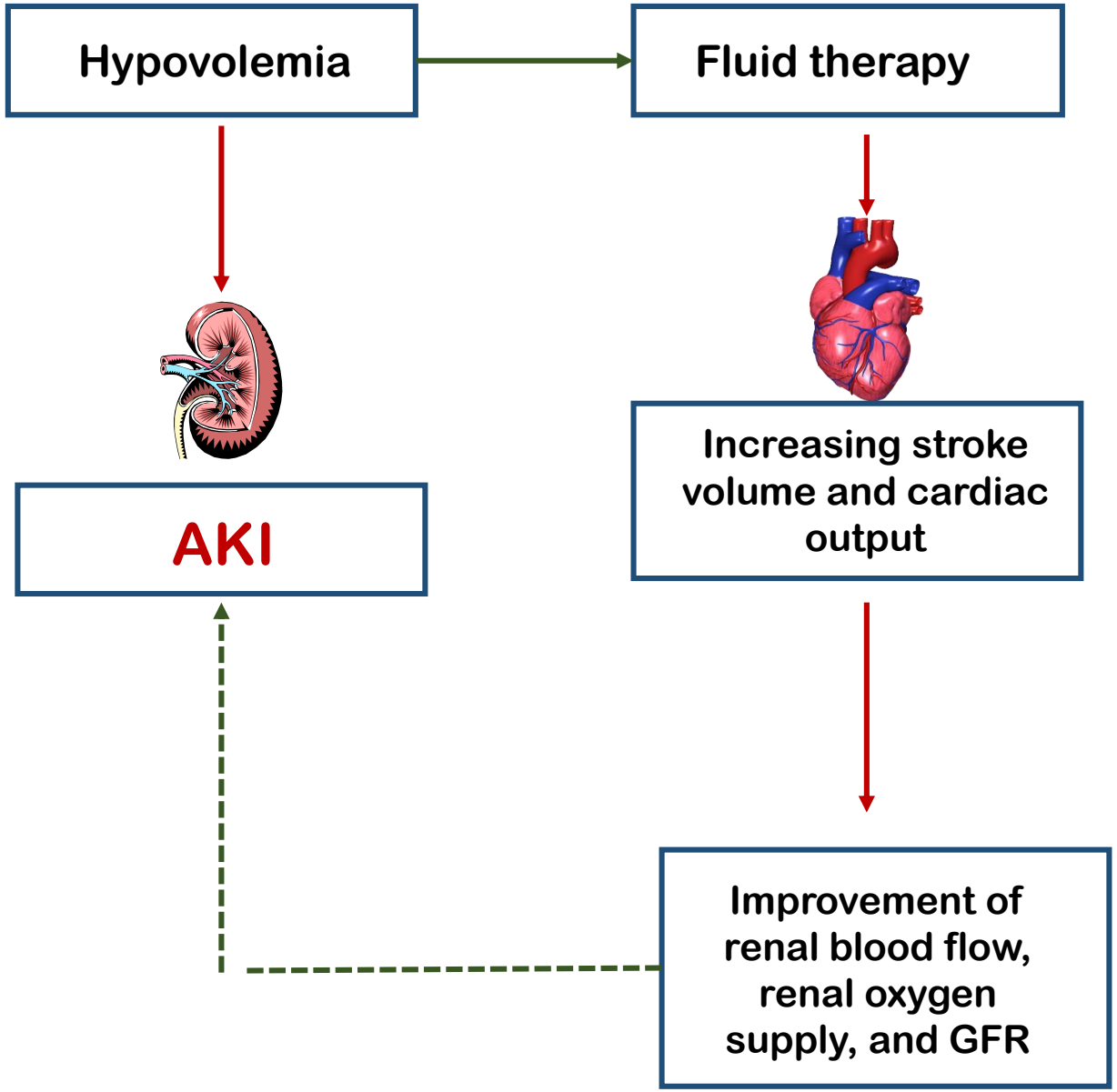
AKI and critical illness

- AKI is a frequent complication in critically ill patients, affecting more than 50% of these patients
- The development of AKI is associated with serious morbidities and high mortality.
- Due to the lack of effective pharmacotherapies, treatment remains supportive and includes optimizing of hemodynamics and fluid status, avoidance of nephrotoxic agents, and in severe cases kidney replacement therapy (KRT).
- Fluid management in critically ill patients with AKI can be difficult because of the frequent association of oliguria or anuria with fluid overload.

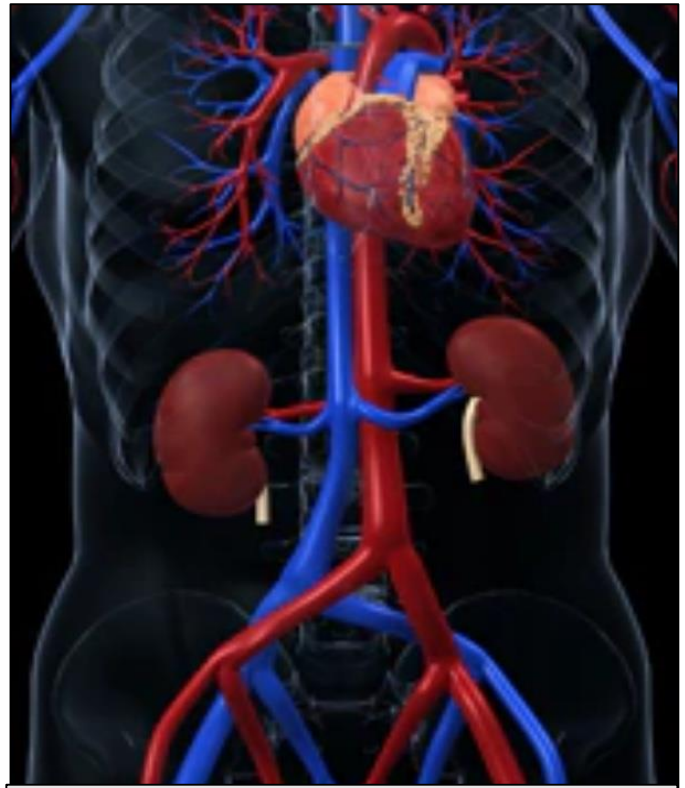
Kidneys receive 20 to 25% of cardiac output (1000 t0 1200 mL/min).



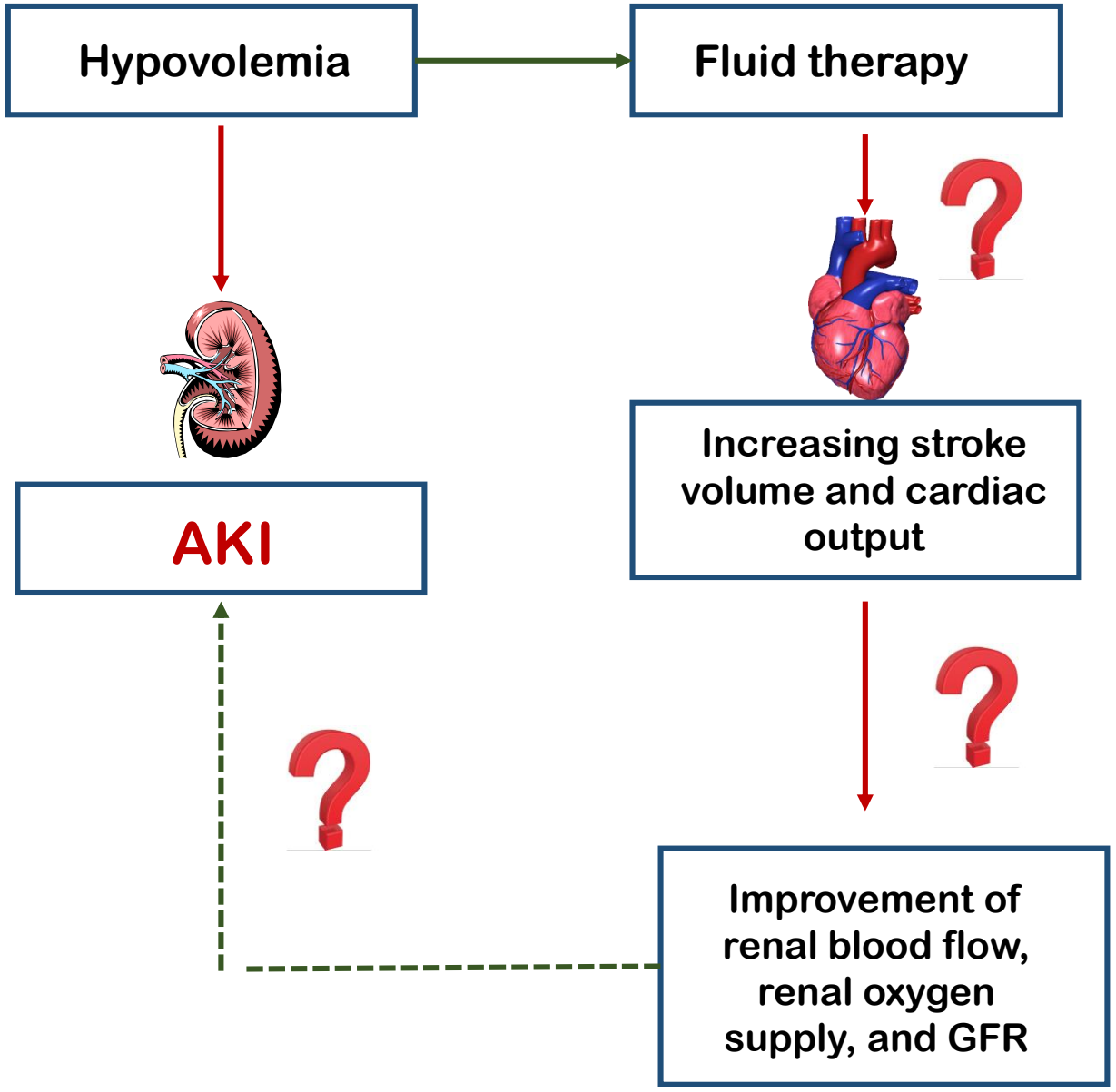
US department of Health and Human Services, NIH



Kidneys receive 20 to 25% of cardiac output (1000 t0 1200 mL/min).



US department of Health and Human Services, NIH



In patients with AKI or at risk of , IV fluids may be inefficient or even harmful.

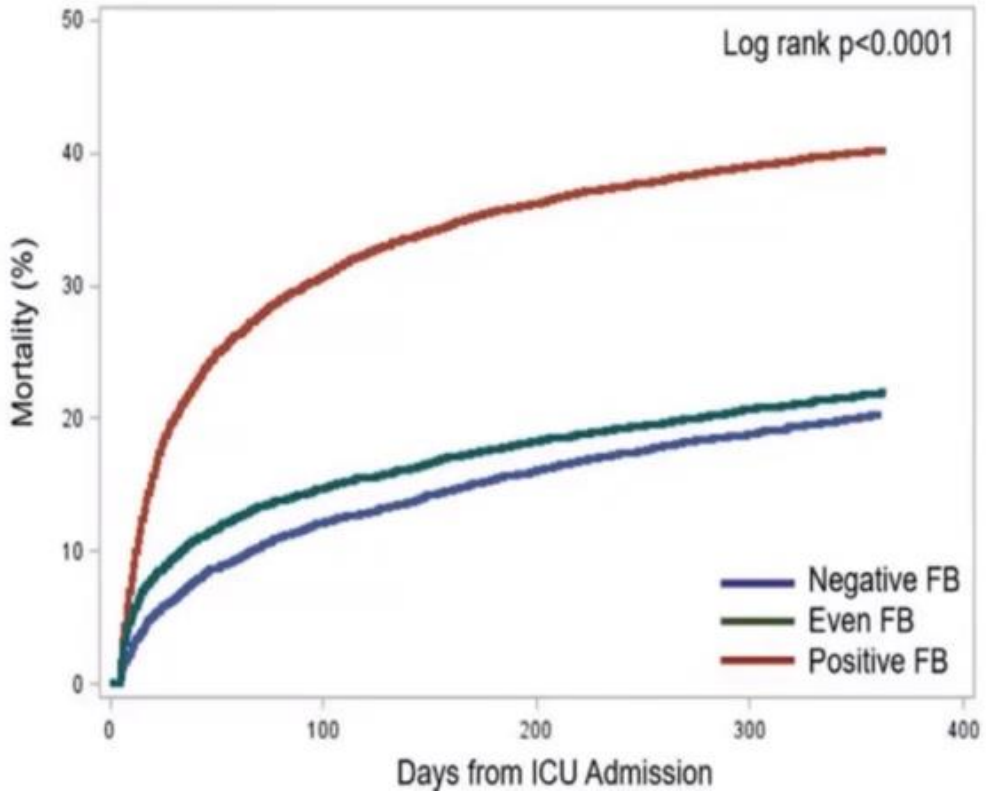
- In established AKI the correlation of renal blood flow (RBF) and GFR is poor.
- AKI can be caused by reasons unrelated to hypovolemia, like exposure to nephrotoxic agents.
- Tubular reabsorption increases by fluid administration leading to an increase in tubular cells workload and O2 consumption.
- Because of the decreased metabolic activity in patients with AKI, intent to maintain or increases renal oxygen delivery by fluid administration is questionable.
- About half of of the oliguric ICU patients are not renal responders. Fluid administration and the resulted volume overload overload may leads to worsening of AKI.

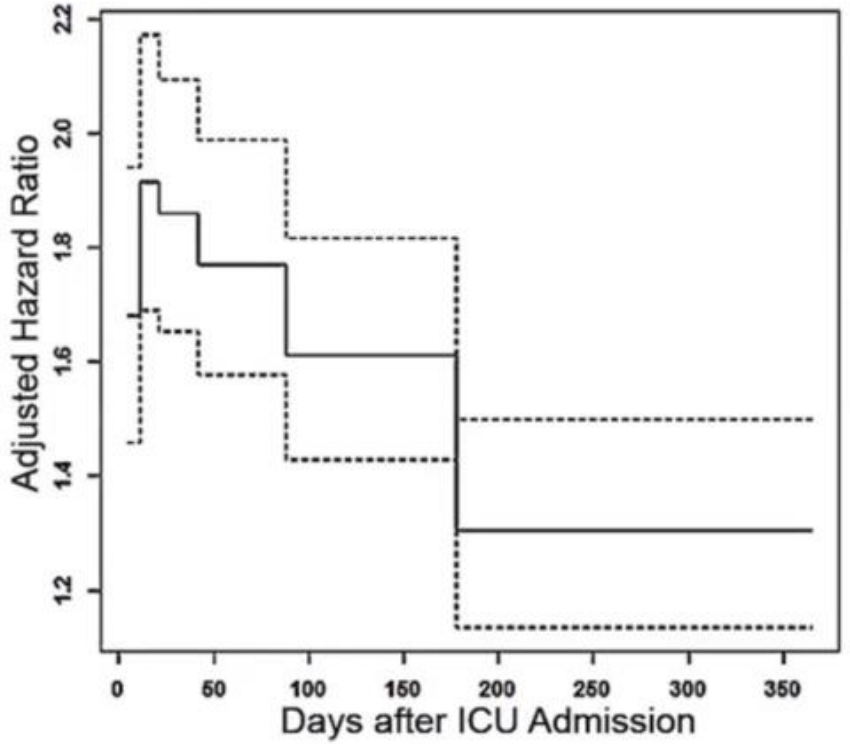
The adverse effects of fluid overload

First author	Patients	Population	Study design	Intervention	Significant results
Simmons, 1987	113	ARDS	prospective cohort	none	higher cumulative fluid balance and weight gain associated with increased mortality
Schuller, 1991	89	pulmonary edema	retrospective cohort	none	higher fluid balance associated with increased mortality, length of hospitalization and days on mechanical ventilation
Goldstein, 2001	21	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Brandstrup, 2003 [3]	172	elective colorectal surgery	randomized controlled trial	restrictive vs. standard perioperative fluid strategy	restrictive strategy reduced cardiopulmonary and tissue-healing complications
Foland, 2004	113	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Gillespie, 2004	77	pediatric AKI	retrospective cohort	none	higher fluid balance associated with mortality
Michael, 2004	26	pediatric AKI	retrospective interventional	percentage of fluid overload <10%	100% of survivors vs. 40% of nonsurvivors had a percentage of fluid <10%
Goldstein, 2005	116	pediatric AKI	prospective cohort	none	higher fluid balance associated with mortality
Sakr, 2005	393	ALI/ARDS	prospective cohort	none	higher fluid balance associated with mortality
Uchino, 2006	331	critically ill	prospective	none	higher fluid balance associated with mortality
Wiedemann, 2006	1,000	ARDS	randomized controlled trial	conservative vs. liberal fluid strategy	conservative strategy improved lung function and shortened the duration of mechanical ventilation
Payen, 2008	1,120	critically ill	prospective cohort	none	higher fluid balance associated with mortality
Bouchard, 2009	618	AKI	prospective cohort	none	higher fluid balance associated with mortality and possibly reduced renal recovery

Bouchard JE and Mehta RL. Contibut Nephrol 2010

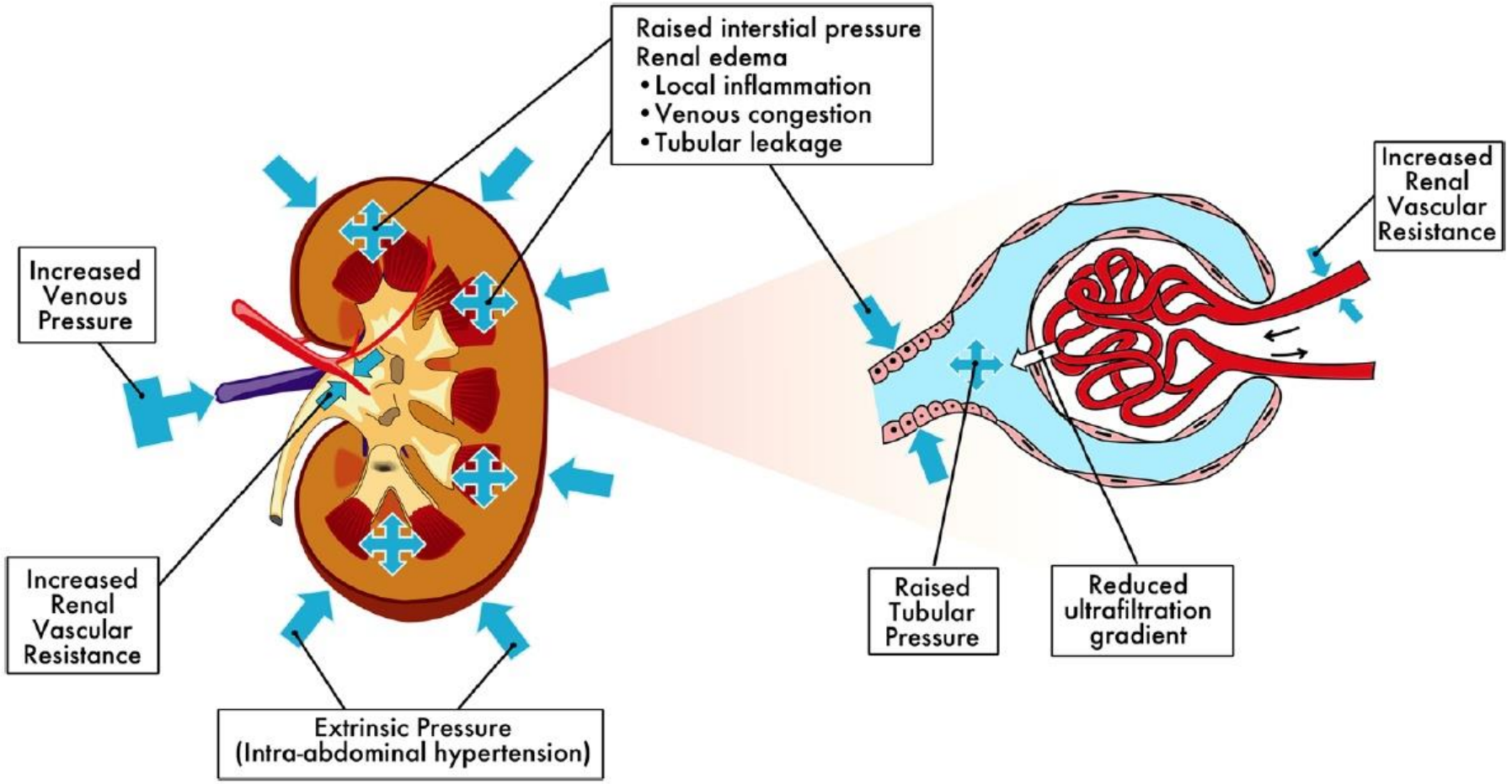
Volume overload and mortality in critically ill patients





Balakumar V. , et al. Crit Care Med 2017

Deteriorating effect of fluid overload on kidney function

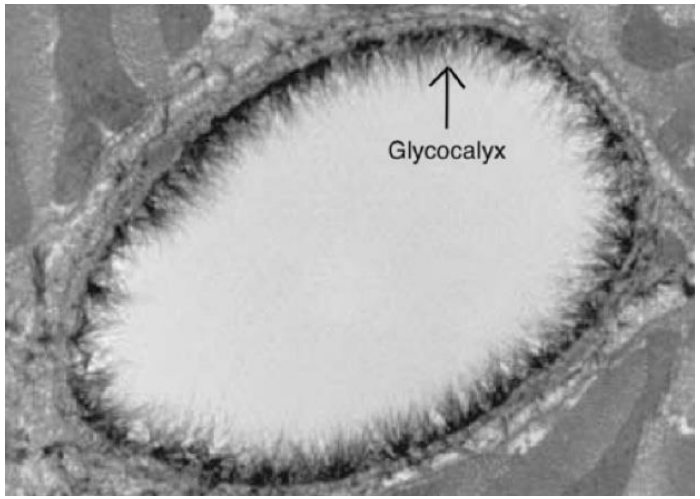


Perner A, et al. Intensive Care Med 2017

Endothelial Glycocalyx

- The endothelial glycocalyx is a network of glycoproteins and proteoglycans covering endothelium.

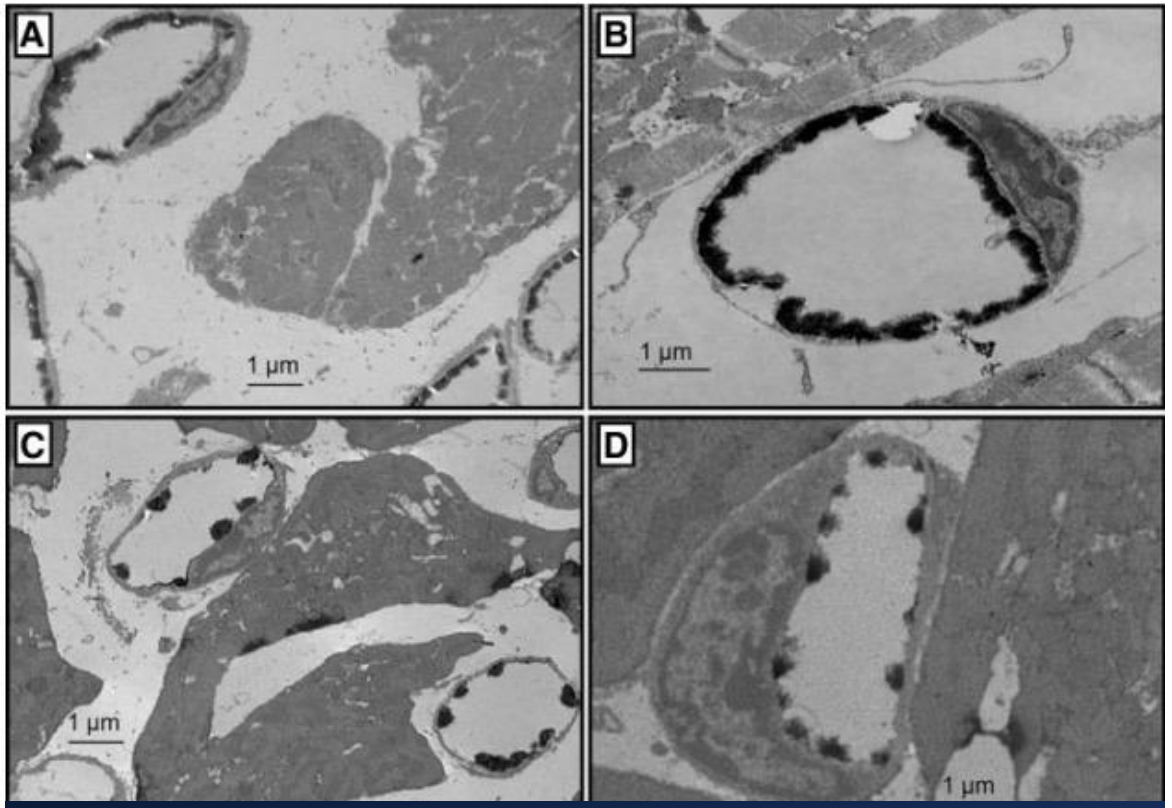
- It prevent leukocyte activation and platelet aggregation and retain plasma proteins and fluids from moving across the endothelium.



Reitsma S., et al. Pflugers Arch 2007

Natriuretic peptides and endothelial Glycocalyx

Natriuretic peptides lead to the shedding of glycocalyx through the cleavage of the membrane-bound proteoglycans, mainly syndecan-1 and hyaluronic acid.

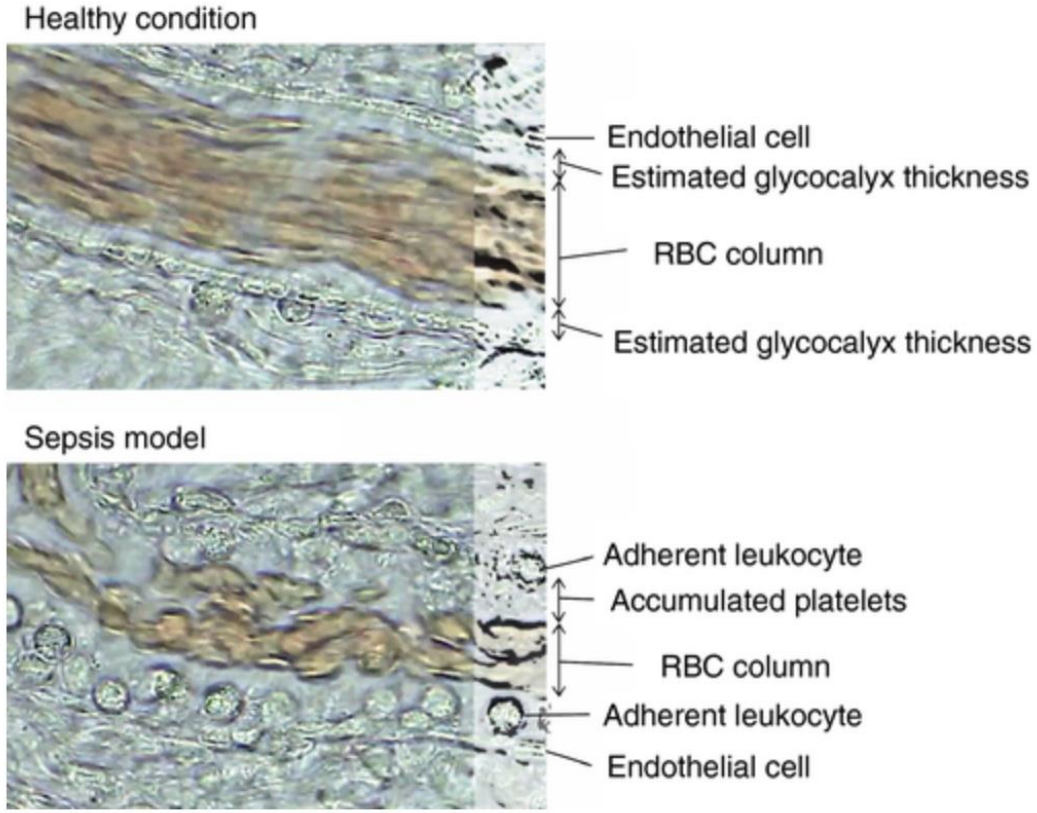


Electron microscopy of isolated Guinea pig hearts
A and B: infusion of HES (hydroxy ethyl starch)
C and D: infusion of HES and ANP

Bruagger D,. et al. Am J Phsiol Heart Circ Physiol 2005

Sepsis and endothelial Glycocalyx

In sepsis and multi-organ failure glycocalyx shedding increases vascular permeability and contributes to fluid leak and activation of immune cascade.

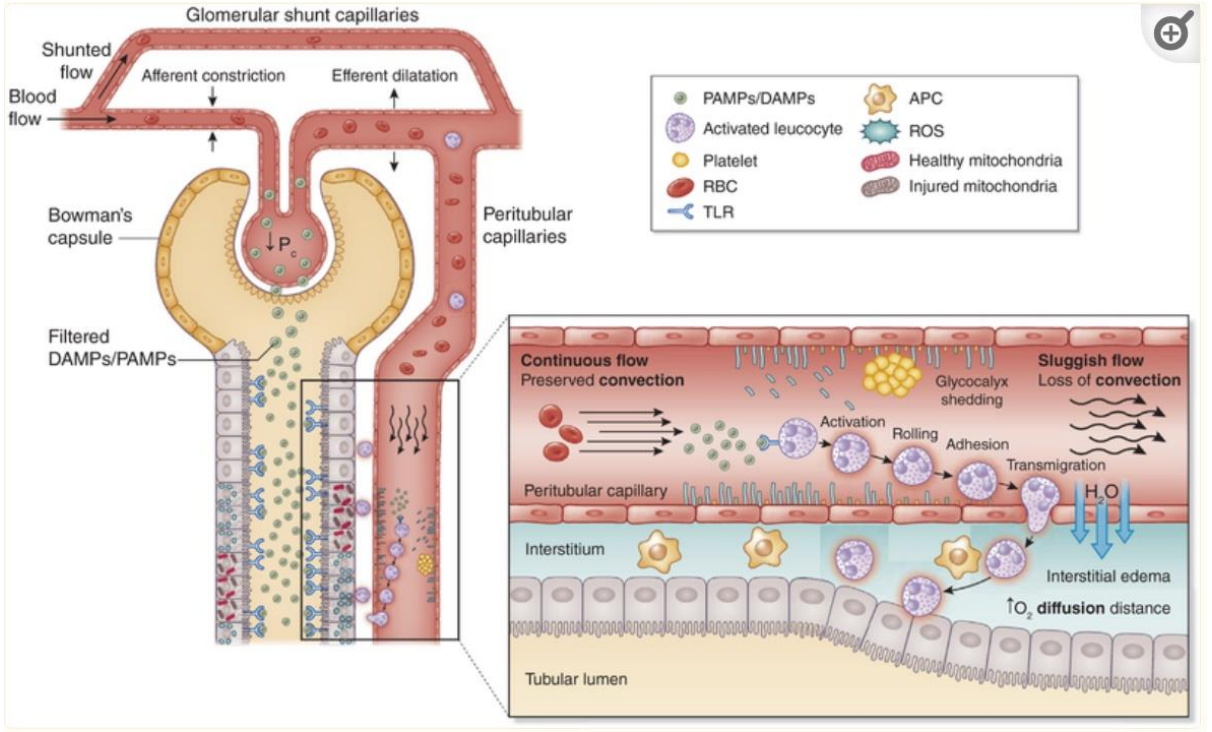


Smooth capillary circulation under normal condition

Change in microcirculation after endotoxin administration

Iba T and Levy JH. J Thromb Haemost 2019

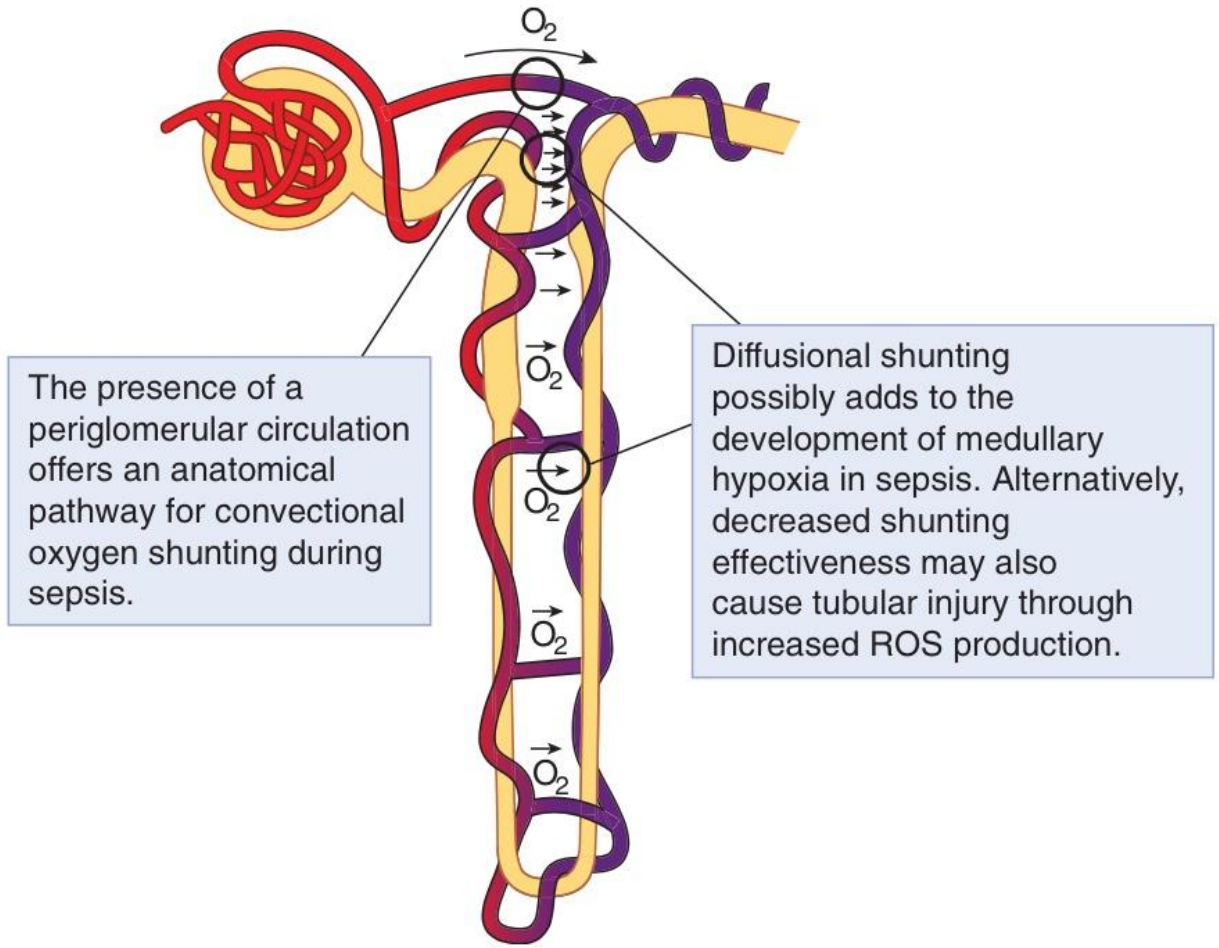
Microcirculatory and inflammatory alternations in sepsis



Decreased GFR and filtration fraction might persist even in adequately resuscitated septic patients due to the altered kidney microcirculation.

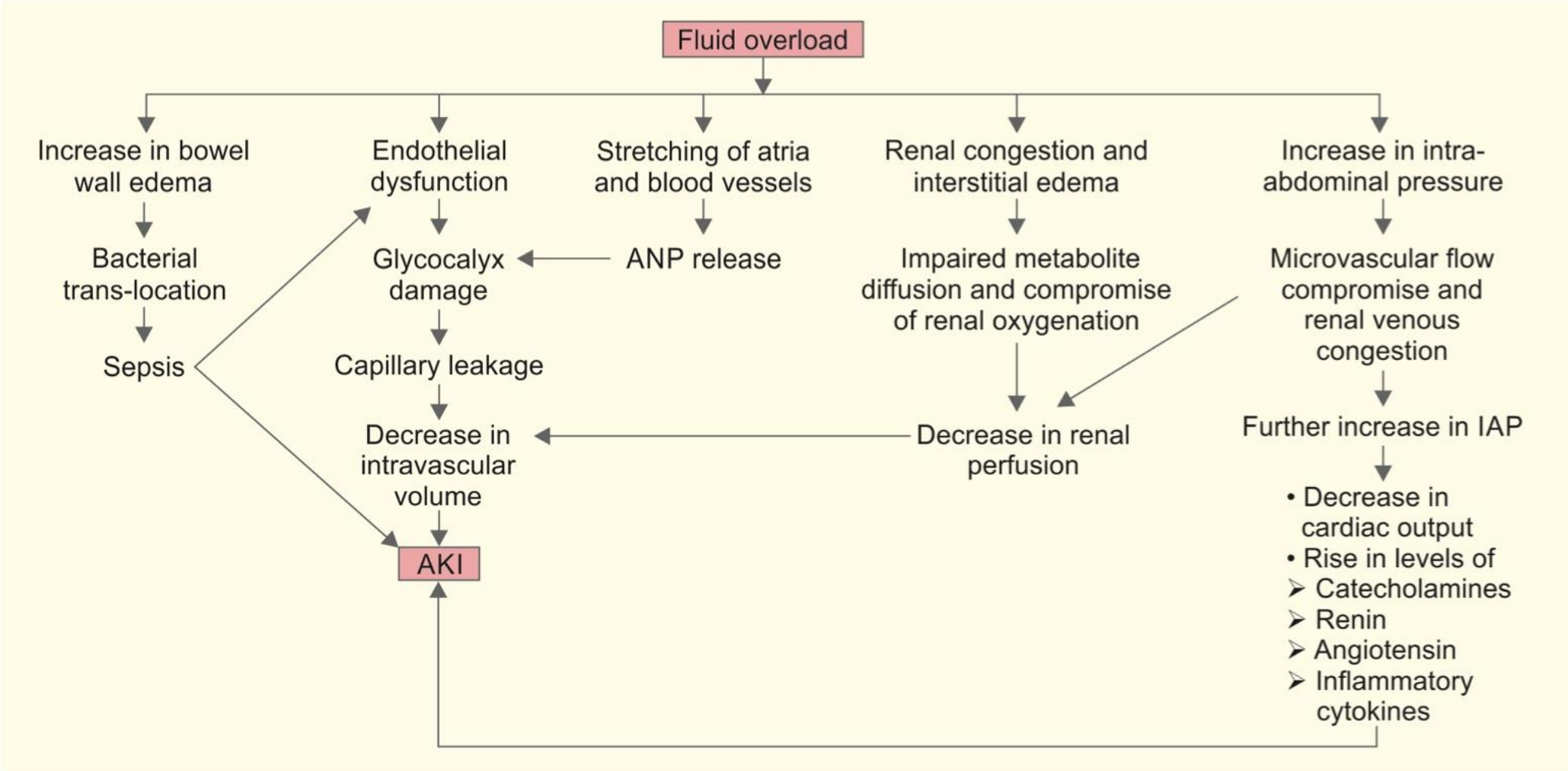
Peerapornatana et al. Kidney Int 2019

Microcirculation and AKI: renal hypo-perfusion even in the absence of hypotension



The kidney's unique vascular anatomical arrangement serves to maintain a stable renal tissue po2 in the presence of variable RBF. Disturbance of the delicate vascular function of kidney likely contributes to the development of renal dysfunction in sepsis.

Post E.H., et al. Kidney Int 2017



Patil V.P. Indian J Crit Care 2020

The adverse effects of fluid overload on patients with AKI

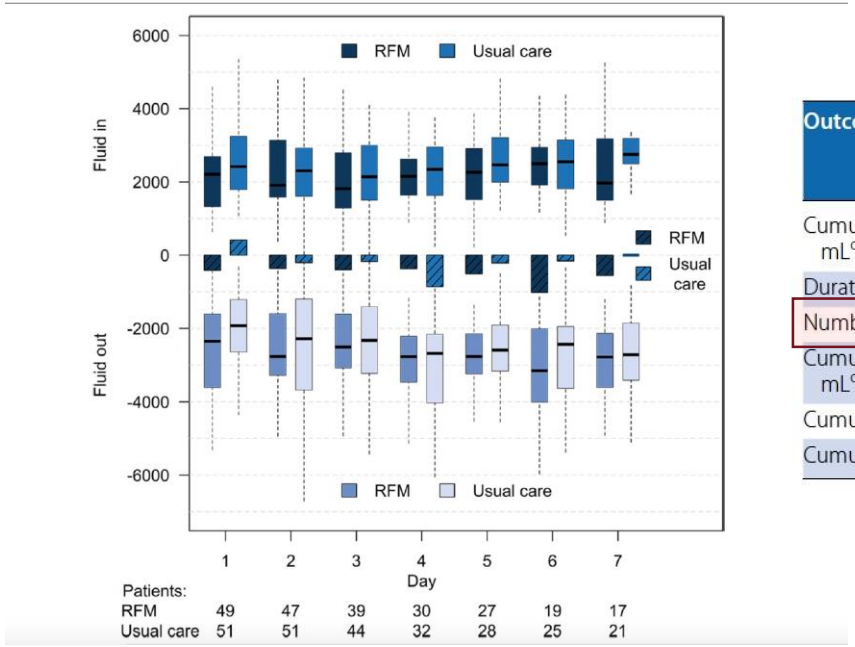
Study	Setting	*n*	Design	Findings
Teixeira *et al.* (2013)[52]	Critically ill adults	601	Secondary analysis of a multicentre observational study	In AKI, higher fluid balance and lower urine volume independently associated with 28-day mortality
Askenazi *et al.* (2013)[130]	Near-term/term sick neonates	58	Prospective single-centre observational study	AKI associated with a net-positive fluid balance and higher mortality
Basu *et al.* (2013)[53]	Paediatric patients undergoing arterial switch operation	92	Retrospective single-centre observational study	AKI associated with higher postoperative day 1 fluid balance and independently associated with prolonged duration of ventilation and hospitalization
Hazle *et al.* (2013)[131]	Infants undergoing congenital heart surgery	49	Prospective single-centre observational study	Fluid overload might be an important risk factor for morbidity at all severities of AKI
Vaara *et al.* (2012)[57]	Critically ill adults with AKI requiring RRT	283	Prospective multicentre observational study	Fluid overload at RRT initiation doubled crude 90-day mortality and remained a significant risk for death after adjustment for demographics and illness severity
Prowle *et al.* (2012)[37]	Studies of perioperative GDT reporting AKI outcomes	24 RCTs	Meta-analysis	GDT significantly reduced risk of postoperative AKI. However, only GDT protocols that were overall fluid neutral were associated with a beneficial renal outcome
Selewski *et al.* (2012)[132]	Paediatric ICU patients requiring ECMO and RRT	53	Retrospective single-centre observational study	Fluid overload at RRT initiation significantly lower in survivors. Correction of fluid overload after initiation of RRT did not improve outcome
Bellomo *et al.* (2012)[62]	Critically ill patients requiring RRT for AKI in the RENAL study	1,453	Retrospective analysis of a multicentre RCT	Negative mean daily fluid balance on RRT consistently associated with risk of death, survival time, RRT-free days, and ICU and hospital-free days
Dass *et al.* (2012)[58]	Cardiovascular surgery patients	94	Retrospective analysis of a single-centre RCT	Positive fluid balance >849 ml in early postoperative period associated with significantly elevated AKI risk
Kambhampati *et al.* (2012)[59]	Adult patients undergoing cardiovascular surgery	100	Prospective single-centre observational study	Progressive severity of positive fluid balance associated with increased AKI risk
Heung *et al.* (2012)[61]	Patients with AKI requiring initiation of RRT	170	Retrospective single-centre observational study	High fluid overload at RRT initiation predicted worse renal recovery at 1 year
Selewski *et al.* (2011)[133]	Critically ill children requiring RRT	113	Retrospective single-centre observational study	Fluid overload at initiation of RRT significantly greater in non-survivors
Grams *et al.* (2011)[55]	Critically ill patients with lung injury enrolled into FACTT	1,000	Retrospective analysis of multicentre RCT	A positive fluid balance after AKI strongly associated with mortality in crude and adjusted analyses; post-AKI diuretic therapy associated with 60 day survival
Fülöp *et al.* (2010)[54]	Critically ill adults with AKI requiring RRT	81	Retrospective single-centre observational study	Volume related weight gain ≥10% and oliguria significantly associated with mortality in multivariable models adjusting for illness severity and diagnosis
Sutherland *et al.* (2010)[56]	Critically ill children with AKI requiring RRT	297	Prospective observational study	≥20% fluid overload at CRRT initiation associated with higher mortality than 10–20% fluid overload, in turn associated with higher mortality than <10% fluid overload; association between degree of fluid overload and mortality remained after adjusting for intergroup differences and severity of illness
Bouchard *et al.* (2009)[51]	Critically ill adults with AKI	618	Secondary analysis of a prospective multicentre observational study	In patients with AKI >10% fluid overload independently associated with 60-day mortality; >10% fluid overload at peak serum creatinine associated with non-recovery of renal function
Payen *et al.* (2008)[50]	Patients enrolled in the SOAP study	3,147	Secondary analysis of a prospective multicentre observational study	Fluid overload an independent risk factor for 60-day mortality in AKI; patients not developing AKI achieved a mean neutral to negative daily fluid balance; AKI associated with daily fluid accumulation

Abbreviations: AKI, acute kidney injury; CRRT, continuous RRT; ECMO, extra-corporeal membrane oxygenation; GDT, goal-directed therapy; ICU, intensive care unit; RCT, randomized controlled trial; RRT, renal replacement therapy.

Prowle J.R., et al. Nature Reviews Nephrology 2014

Restrictive fluid management versus usual care in AKI (REVERSE-AKI trial)

A multicenter pilot randomized controlled trial on 100 patients with AKI in five European and two Australian ICUs



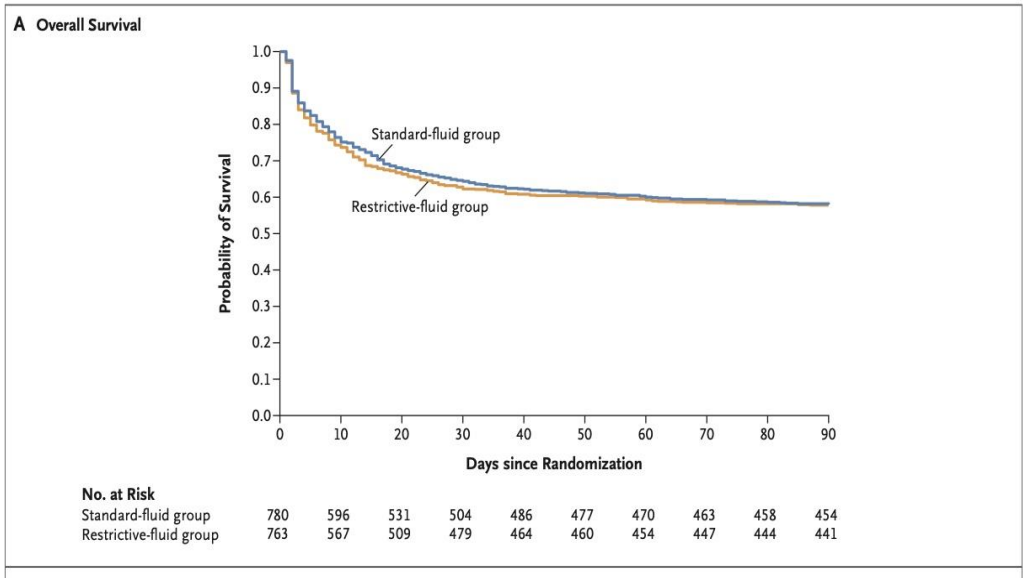
Outcome	Restrictive fluid management ($n=49$)	Usual care ($n=51$)	Restrictive fluid management vs usual care (95% CI)[a]	*P* value[b]
Cumulative fluid balance at 72 h from randomization, mean (SD) mL[c]	−1080 (2003)	61 (3131)	−1148 (−2200; −97)	0.033
Duration of AKI (days), median [IQR][d]	2 [1–3]	3 [2–7]	−1 (−3; 0)	0.071
Number of patients-receiving RRT, n (%)[e]	6/46 (13)	15/50 (30)	0.42 (0.16; 0.91)	0.043
Cumulative fluid balance at 24 h from randomization, mean (SD) mL[c]	−416 (1194)	409 (1566)	−822 (−1381; −264)	0.004
Cumulative fluid balance at ICU discharge/day 7, mean (SD) mL[c]	−2166 (2988)	−650 (4469)	−1532 (−3036; −29)	0.046
Cumulative dose of furosemide per day, median [IQR] mg[f]	0 (0–19)	1.4 (0–26.2)	0 (−11; 5.7)	0.700

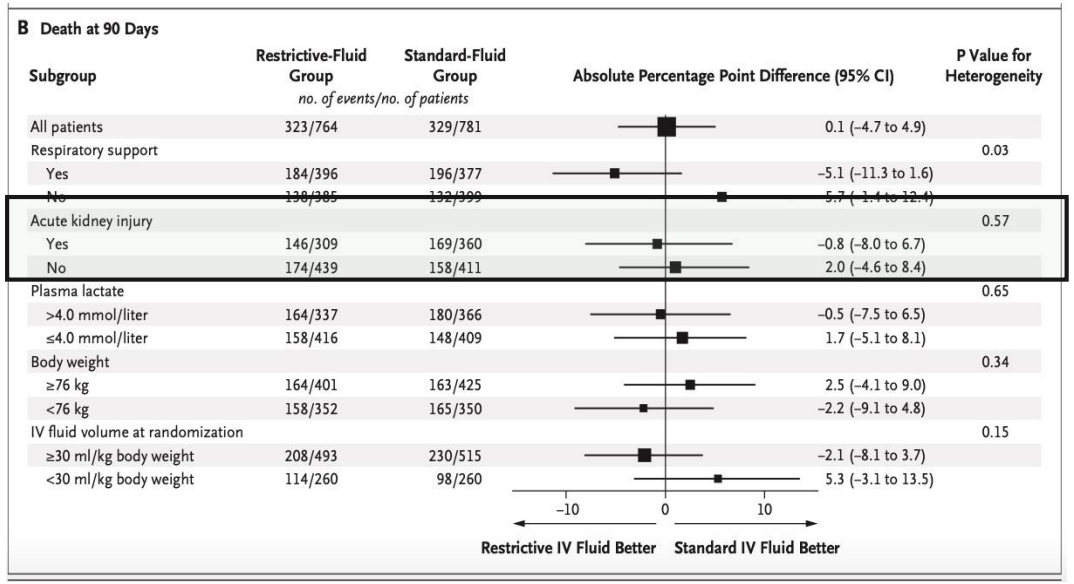
A restrictive fluid management strategy aiming neutral or negative fluid balance after initial resuscitation in patients with AKI is feasible and probably associated with less adverse events.

Vaara S.T., et al. Intensive Care Med Med 2021

Restriction of intravenous fluid in ICU patients with septic shock (CLASSIC trial)

An international RCT on 1545 patient with septic shock





Among adult patients with septic shock in the ICU, restrictive fluid strategy did not result in fewer death at 90 days than standard intravenous fluid therapy. The rates of AKI were not significantly different in two arms of the study.

Meyhoff T.S., et al. New Engl J Med 2022

Back to patient

The doses of vasopressor and inotrope medications were reduced within 24 hours to keep MAP> 65 mmHg. The patient was weaned from the mechanical ventilation after 48 hours, and oral nutrition was started. The intravenous volume was 2.5 L of normal saline per day. By the development of dyspnea on the second day, the oxygen flow increased to 6 L/min. At the time of nephrology consultation on the third day of ICU admission, his urine output had been decreased to 300 mL for the previous 12 hours. Chest-x-ray revealed diffuse bilateral infiltration. Other findings included the followings:

- BP: 100/70 (dependent to vasopressors/inotropes)
- Peripheral edema: +3
- Cumulative fluid balance: +8 lit
- Hgb: 10.3 g/dL, HCT: 30%
- BUN: 120 mg/dL
- Creatinine: 3.5 mg/dL
- Na:136 mEq/L
- K: 4.8 mEq/L
- CL: 110 mEq/L
- PH: 7.08, HCO3: 10 mEq/L

- Cumulative fluid balance divided by baseline fluid weight multiplying by one hundred: (8/75) x100 = 10.7%
- The patient is fluid overload (the increase of >10% fluid accumulation)

Oliguria should trigger an assessment of fluid status but NOT be considered as an absolute indication for fluid administration. The only indication for fluid administration in AKI is volume depletion.

Journal of Critical Care 71 (2022) 154070

Contents lists available at ScienceDirect

Journal of Critical Care

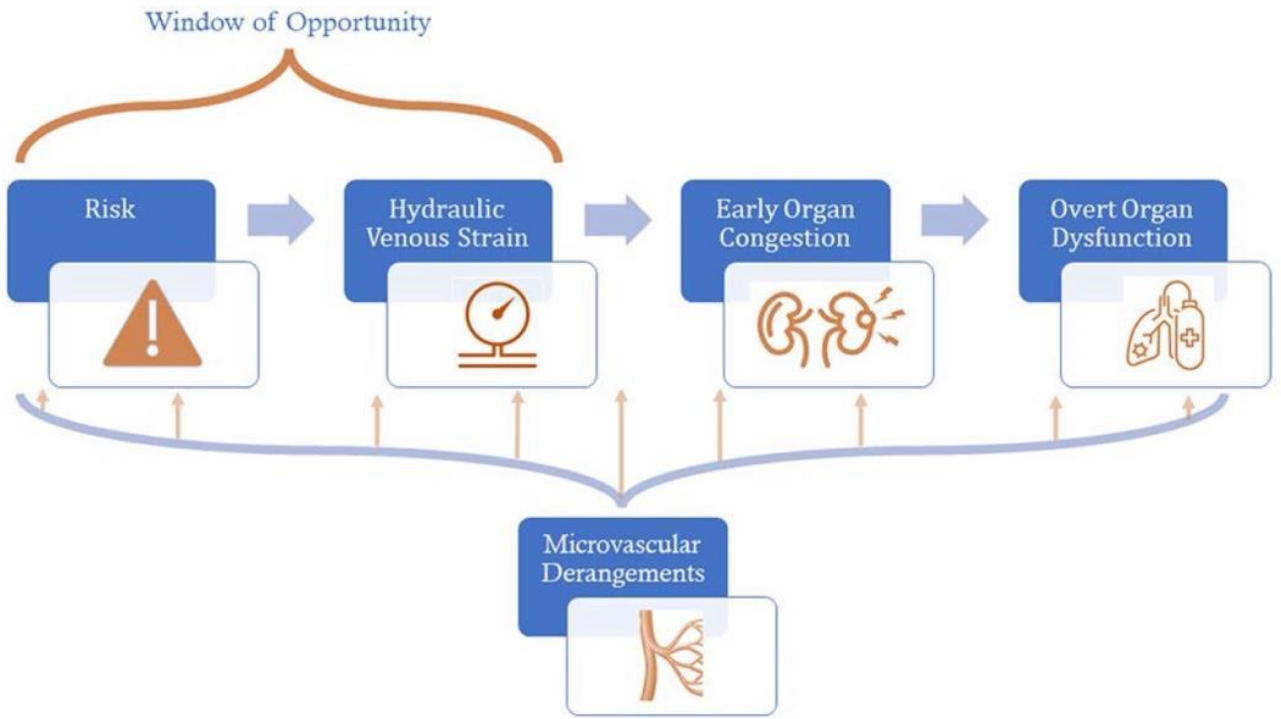
journal homepage: www.journals.elsevier.com/journal-of-critical-care

The emerging concept of fluid tolerance: A position paper

Eduardo Kattan [a], Ricardo Castro [a], Francisco Miralles-Aguiar [b], Glenn Hernández [a], Philippe Rola [c,*]

[a] Departamento de Medi ntensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile
[b] Anesthesia & Surgery C l Care Service, Hospital Universitario Puerta del Mar, Cádiz, Spain
[c] Chief of Service, Intensive Care Unit, Hopital Santa Cabrini, CIUSSS EMTL, Montreal, Canada

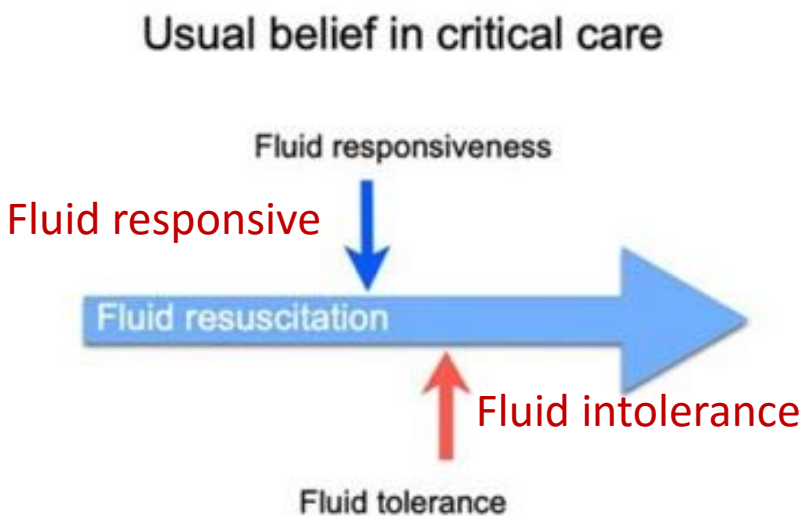
Conceptual model of fluid induced harm in critically ill patients

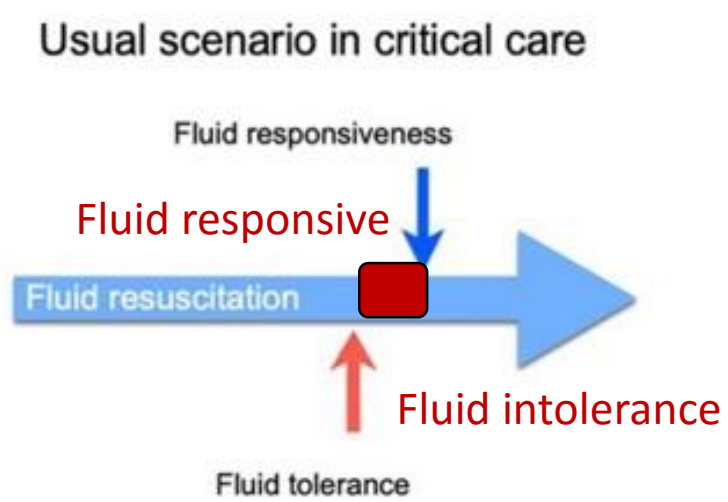


- Few strategies have addressed the impact of fluids on the venous side, that may lead to congestion and organ dysfunction.

- Even in fluid responsive patients, fluid administration could be detrimental, depending on the clinical scenario.

Kattan R., et al. Journal of Critical care 2022





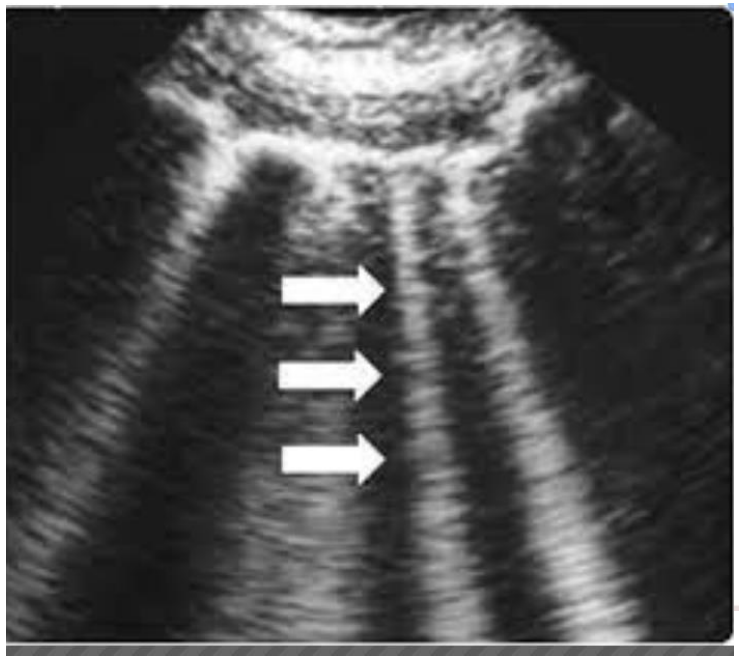
Kattan R., et al. Journal of Critical care 2022

Characteristic	Fluid responsiveness	Fluid tolerance	Fluid overload
Definition	Increase on cardiac output ≥10% after preload incrementation by manipulation of venous return in a dynamic test context.	Fluid tolerance is the degree to which a patient can tolerate administration of fluids without causation of organ dysfunction.	A state of global body accumulation of fluids after resuscitation with a deleterious impact on organ function.
When to use	During resuscitation	During resuscitation	After resuscitation
Adequate use	Increase CO through a fluid challenge in FR+ patients to resolve hypoperfusion	Modify resuscitation strategy (vasopressors, other types of fluids, etc.)	Prompt de-resuscitation
Inadequate use	Consider fluid responsiveness as a mandatory trigger for fluid administration, irrespective of tissue perfusion status	Assume that fluid intolerance only occurs in fluid unresponsive patients	Inadequate timing or intensity of de-resuscitation
Limitations	Not assessable in all patients and technical challenges	Theoretical construct, not clinically validated yet	Retrospective diagnosis; still lack of evidence on how to best de-resuscitate

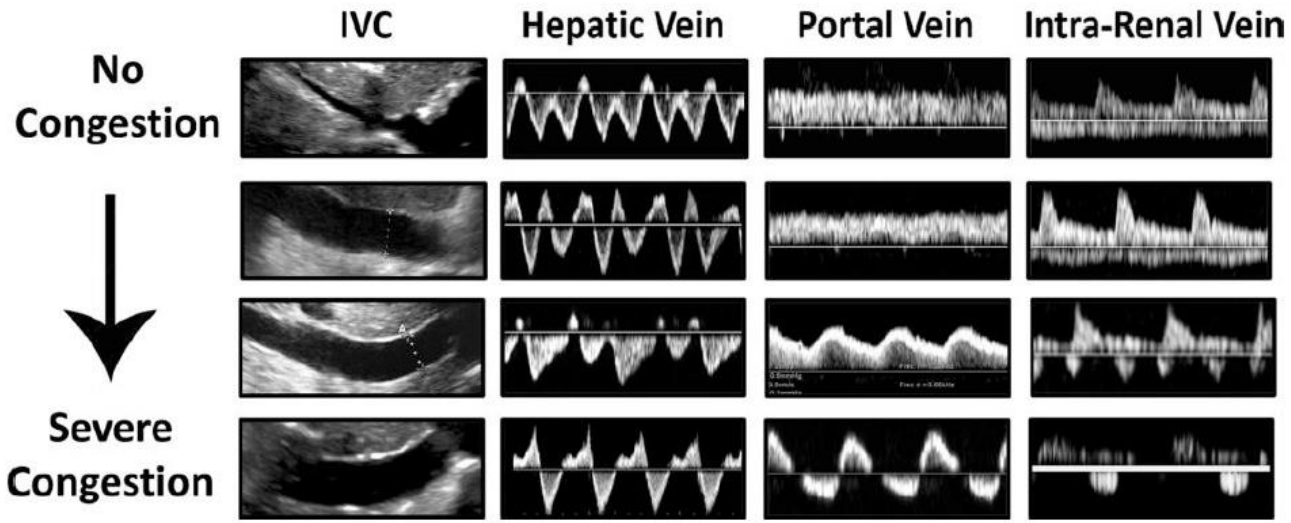
Kattan R., et al. Journal of Critical care 2022

Factors that affect fluid tolerance

- Age
- CKD
- Chronic pulmonary disease
- Abdominal compartment syndrome
- Capillary leak
- Cardiac disease

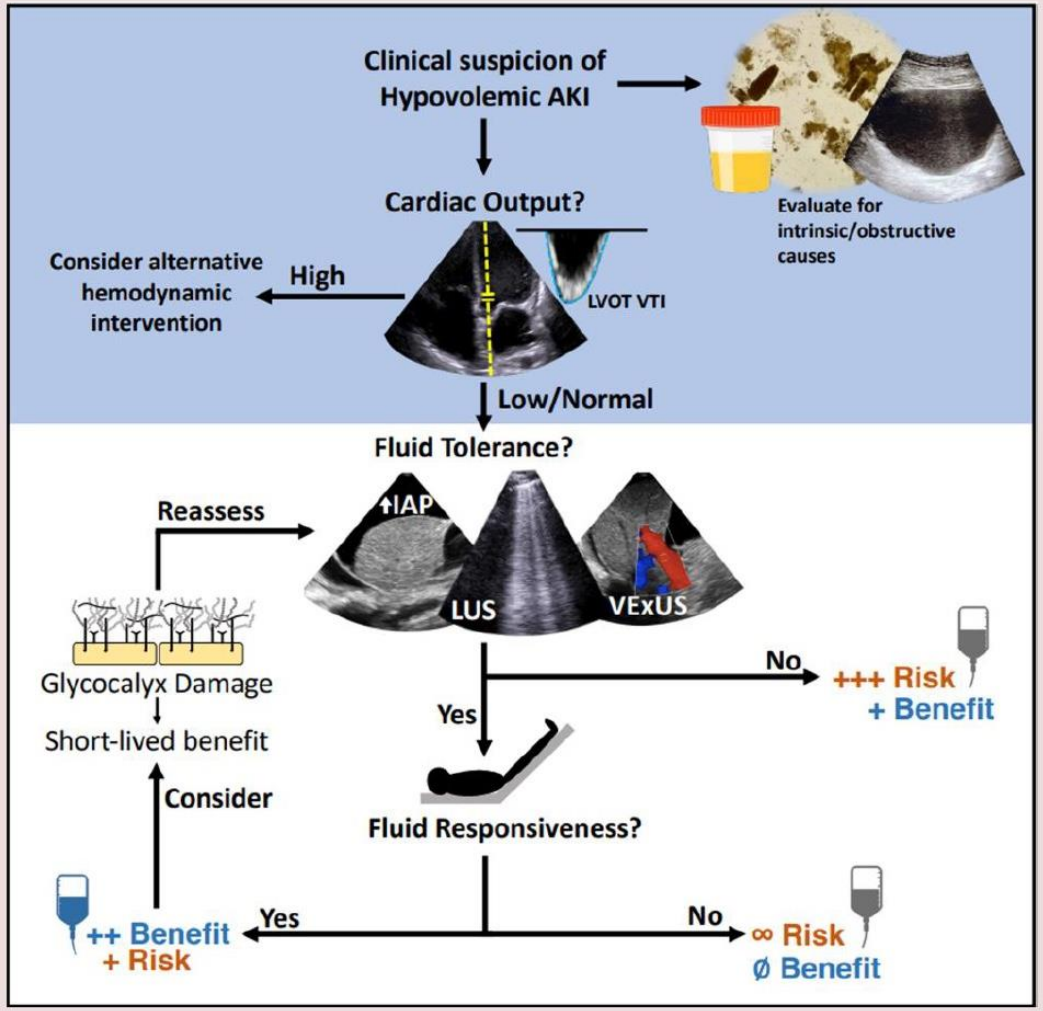


Evaluating lung water by ultrasound (B-lines)



Evaluating systemic venous congestion by Venous Excess Ultrasound Score (VExUS)

Argaiz E.R., et al. European Heart Journal: Acute Cardiovascular Care care 2022



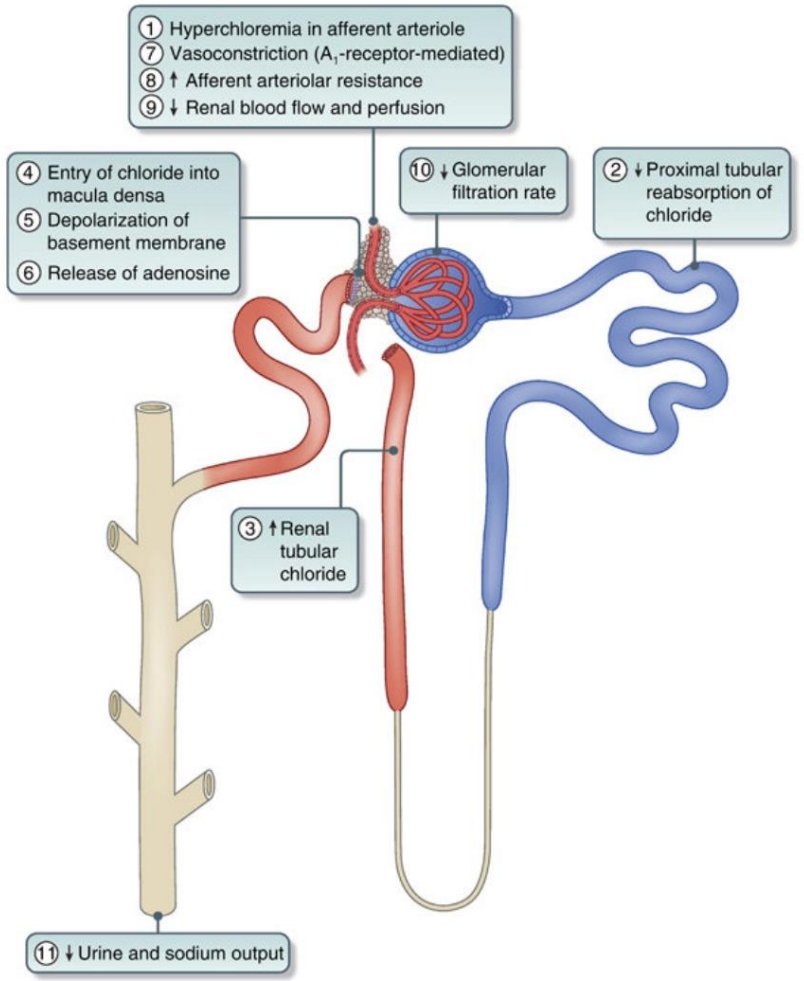
Approach to fluid therapy in acute kidney injury. AKI, acute kidney injury; IAP, intra-abdominal pressure; LUS, lung ultrasound; LVOT VTI, left-ventricular outflow tract velocity–time integral; VExUS, venous excess ultrasound score.

Argaiz E.R., et al. European Heart Journal: Acute Cardiovascular Care care 2022

Isotonic saline **Balanced crystalloids**

	Human plasma	0.9% Sodium chloride	Hartmann's	Ringer's lactate	Ringer's acetate	Plasma-Lyte 148	Plasma-Lyte A pH 7.4	Sterofundin/ Ringerfundin
Osmolarity (mOsm/l)	275–295	308	278	273	276	295	295	309
pH	7.35–7.45	4.5–7.0	5.0–7.0	6.0–7.5	6.0–8.0	4.0–8.0	7.4	5.1–5.9
Sodium (mmol/l)	135–145	154	131	130	130	140	140	145
Chloride (mmol/l)	94–111	154	111	109	112	98	98	127
Potassium (mmol/l)	3.5–5.3	0	5	4	5	5	5	4
Calcium (mmol/l)	2.2–2.6	0	2	1.4	1	0	0	2.5
Magnesium (mmol/l)	0.8–1.0	0	0	0	1	1.5	1.5	1
Bicarbonate (mmol/l)	24–32							
Acetate (mmol/l)	1	0	0	0	27	27	27	24
Lactate (mmol/l)	1–2	0	29	28	0	0	0	0
Gluconate (mmol/l)	0	0	0	0	0	23	23	0
Maleate (mmol/l)	0	0		0		0	0	5
Na:Cl ratio	1.21:1 to 1.54:1	1:1	1.18:1	1.19:1	1.16:1	1.43:1	1.43:1	1.14:1

Crystalloids and AKI: the effect of chloride on kidney



Administration of isotonic saline may reduce GFR and lead to a longer period of fluid retention compared with buffered crystalloids.

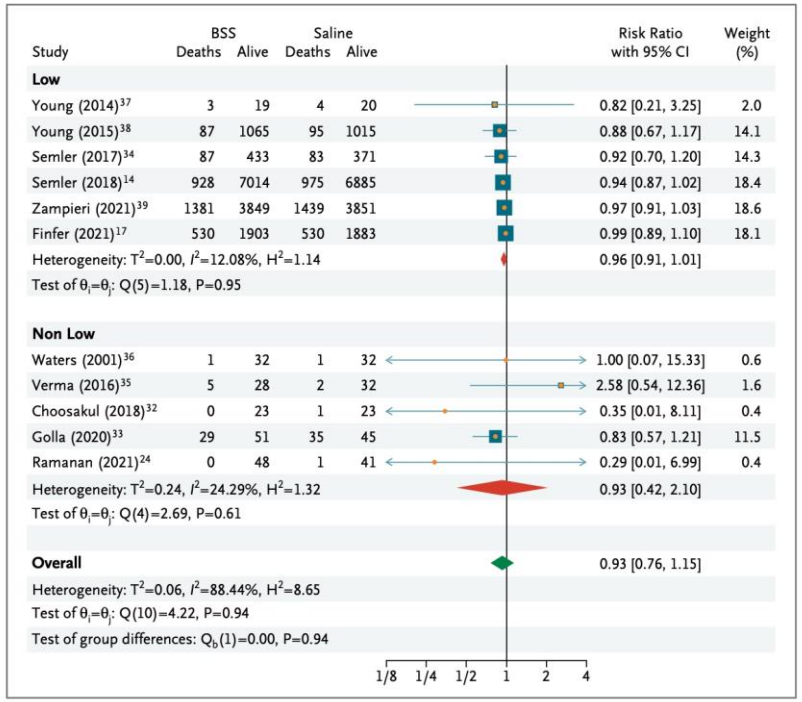
Lobo D.N., and Awad Sh. Kidney Int 2014

Important studies comparing the effect of balanced crystalloids with saline on patient outcomes

	SPILIT trial [1]	SMART trial [2]	SALTED-ED trial [3]	BaSICS trial [4]	PLUS trial [5]
Study type	RCT Double blind	RCT non-blind	RCT non-blind	RCT Double blind	RCT Double blind
Publication year	2015	2018	2018	2021	2022
Population setting	ICU patients	ICU patients	ED patients	ICU patients	ICU patients
Number of participants	2278	15,802	13,347	11,052	5037
Balanced crystalloid	Plasma-Lyte 148	Ringer's Lactate Plasma-Lyte A	Ringer's Lactate Plasma-Lyte A	Plasma-Lyte 148	Plasma-Lyte 148
Primary outcomes	AKI	Major advance kidney event within 30 days	Hospital free days to day 28	90-day survival	90-day survival
Key findings	No difference in the incidence of AKI, RRT use or in hospital mortality	Lower rate of in hospital death, RRT use, or final C≥ 200% of baseline with balanced crystalloid No different in ICU free days and ventilator free day	No difference in hospital free days Lower rate of in hospital death, RRT use, or final C≥ 200% of baseline with balanced crystalloid	No difference in 90-day survival No difference in the incidence of AKI, need for KRT. The 90-day mortality rate was significantly higher in patients with traumatic brain injury receiving balanced crystalloid	No difference in preventing AKI or decreasing all-cause-mortality. The mean, peak, and rise in serum creatinine, as well as the need for initiation of RRT.

1. Young P., et al . JAMA 2015, 2. Semler MW, et al. N Engl J Med 2018 , 3. Self W.H., et al. N Engl J Med 2018,, 4. :Zampieri FG, et al. JAMA 2021, 5. Finfer S., et al. Nengl J Med 2022

A recent meta-analysis evaluating the effect of balanced crystalloids compared with saline

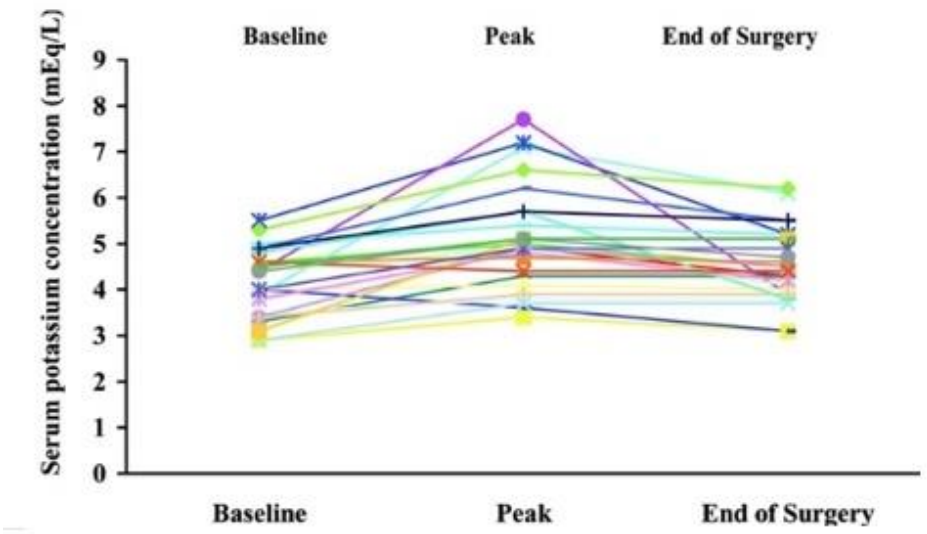


Outcome	Trials (n)	Participants (n)	τ^2	I^2 (%)	Effect measure (RR* or MD†)	95% CI
Secondary outcomes						
Treated with renal replacement therapy	5	33,554	0.02	59.5	0.95	0.81 to 1.11
Incidence of acute kidney injury	5	25,224	0.00	8.6	0.96	0.89 to 1.02
Ventilator-free days (to day 28)	5	32,191	0.32	79.5	0.18‡	−0.45 to 0.81
Vasopressor-free days (to day 28)	3	21,622	0.02	24.1	0.19‡	−0.13 to 0.51
Patient-level subgroup analysis for the primary outcome						

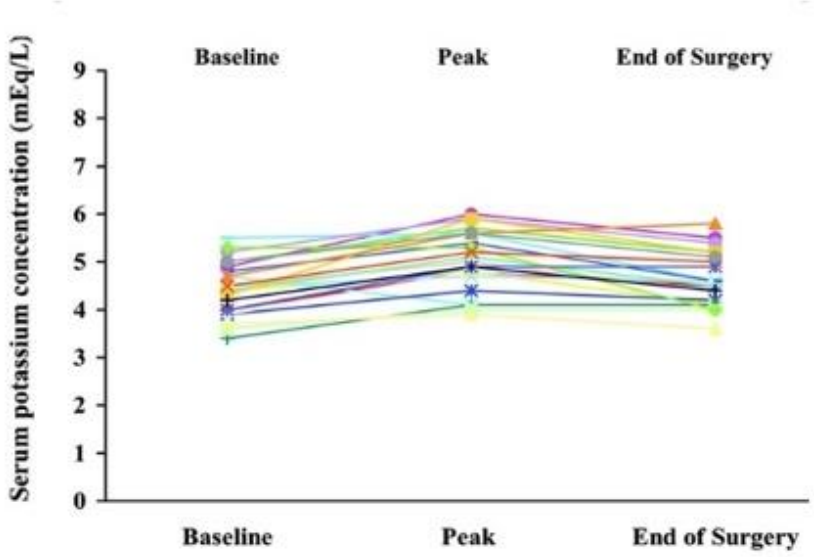
- In this study, among 35,884 patients, the effect of balanced crystalloids ranged from 9% relative reduction to 1% relative increase in 90-days mortality.
- The risk of AKI was similar in both groups. However, in a subgroup of 6754 patients with sepsis, there was a potential benefit for balanced crystalloids.

Hammond NE, et al. NEJM Evid 2022

The risk of hyperkalemia by using 0.9% saline vs Ringer's lactate



Perioperative potassium concentration in patients treated with 0.9% saline

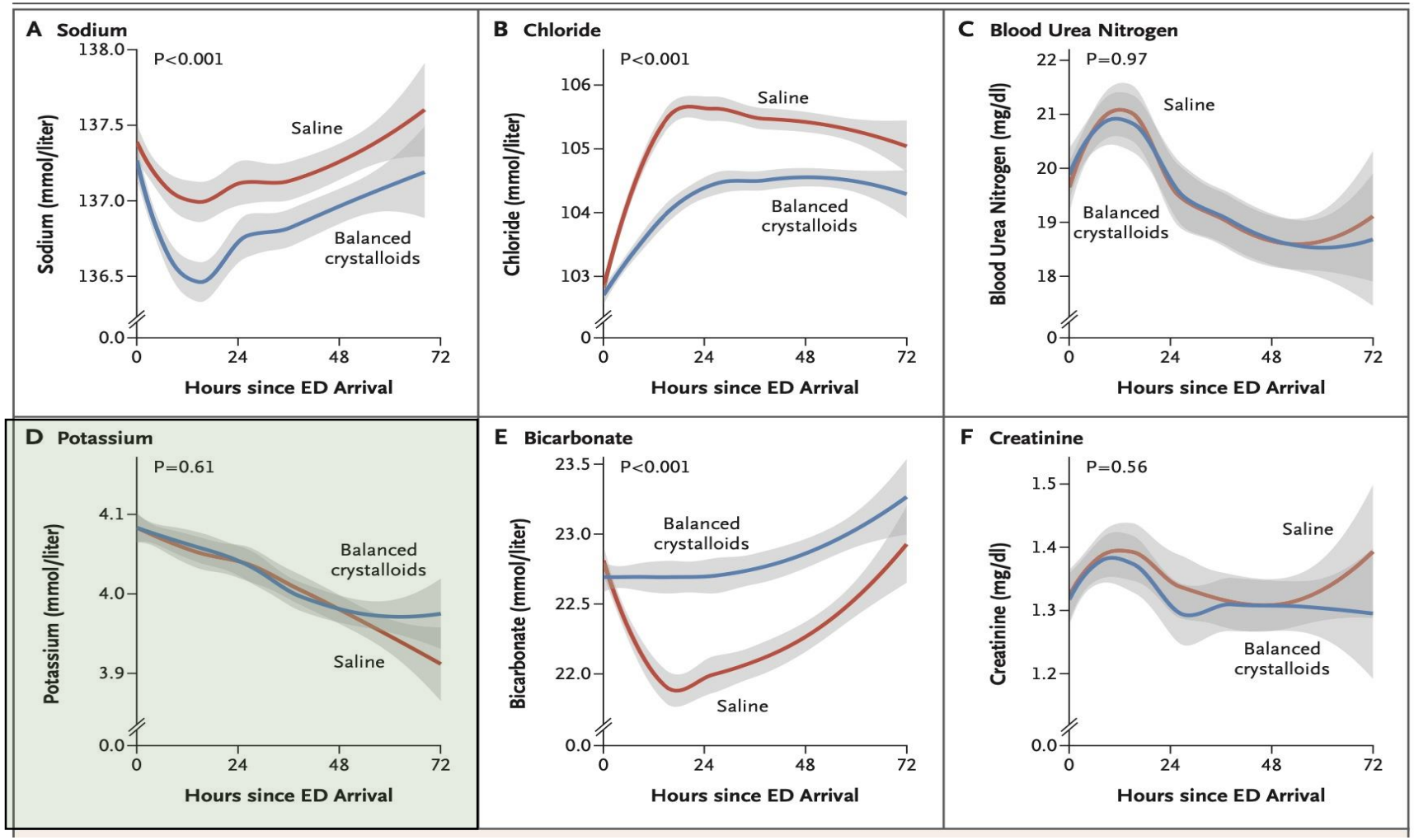


Perioperative potassium concentration in patients treated with Ringer's lactate

Interestingly, a higher risk of hyperkalemia has been reported by O'Malley et al in post-kidney transplant patients who received 2 L of 0.9% saline vs Ringer's lactate. Efflux of intracellular potassium due to acidosis created by chloride-rich crystalloids is a possible explanation.

O'Malley C.M., et al . Anest analg 2005

In SPILIT trial, there was no difference in the serum potassium level of patients who received saline vs balanced crystalloids



Young P., et al . JAMA 2015

Back to patient

The doses of vasopressor and inotrope medications were reduced within 24 hours to keep MAP> 65 mmHg. The patient was weaned from mechanical ventilation after 48 hours, and oral nutrition was started. The intravenous volume was 2.5 L of normal saline per day. After the development of dyspnea after the weaning, the oxygen flow increased to 6 L/min. At the time of nephrology consultation on the 3th day of ICU admission, his urine output had been decreased to 300 mL for the previous 12 hours. Chest-x-ray revealed diffuse bilateral infiltration. Other findings included the followings:

- BP: 100/70 (dependent to vasopressors/inotropes)
- Peripheral edema: +3
- Cumulative fluid balance: +8 lit
- Hgb: 10.3 g/dL, HCT: 30%
- BUN: 120 mg/dL
- Creatinine: 3.5 mg/dL
- Na:136 mEq/L
- K: 4.8 mEq/L
- CL: 110 mEq/L
- PH: 7.08, HCO3: 10 mEq/L

- In patients with hyperchloremia isotonic saline is not recommended
- Probably in patients with sepsis balanced crystalloids are preferred.

Administration of colloids and AKI

Hydroxyethyl starches	As several RCTs and systematic reviews showed increased rates of AKI in critically ill patients receiving hydroxyethyl starches, they are not recommended in these patients.
Gelatin-based colloids	There are only limited data regarding nephrotoxicity of gelatin-based colloids. The potential risks and the absence of clear benefits indicate that gelatin-based fluids should be avoided in AKI.
Albumin	Albumin is probably safe in patients with or at risk of AKI. It has been shown that in patients with hepatorenal syndrome, the combination of albumin with a vasopressor analogues may be reno-protective.

Ostermann M., et al. Chest 2019

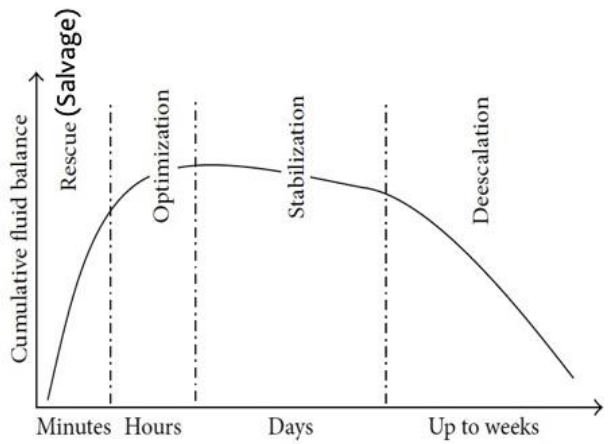
Dos and Don’ts of fluid management in AKI

Factor	Do	Don’t
Indication	Intravascular hypovolemia	Oliguria without hypovolemia
Type of fluid	Crystalloids	Starches
Volume	Boluses of small aliquots	High volumes
Duration	Until hypovolemia corrected	Until AKI resolved

Ostermann M., et al. Chest 2019

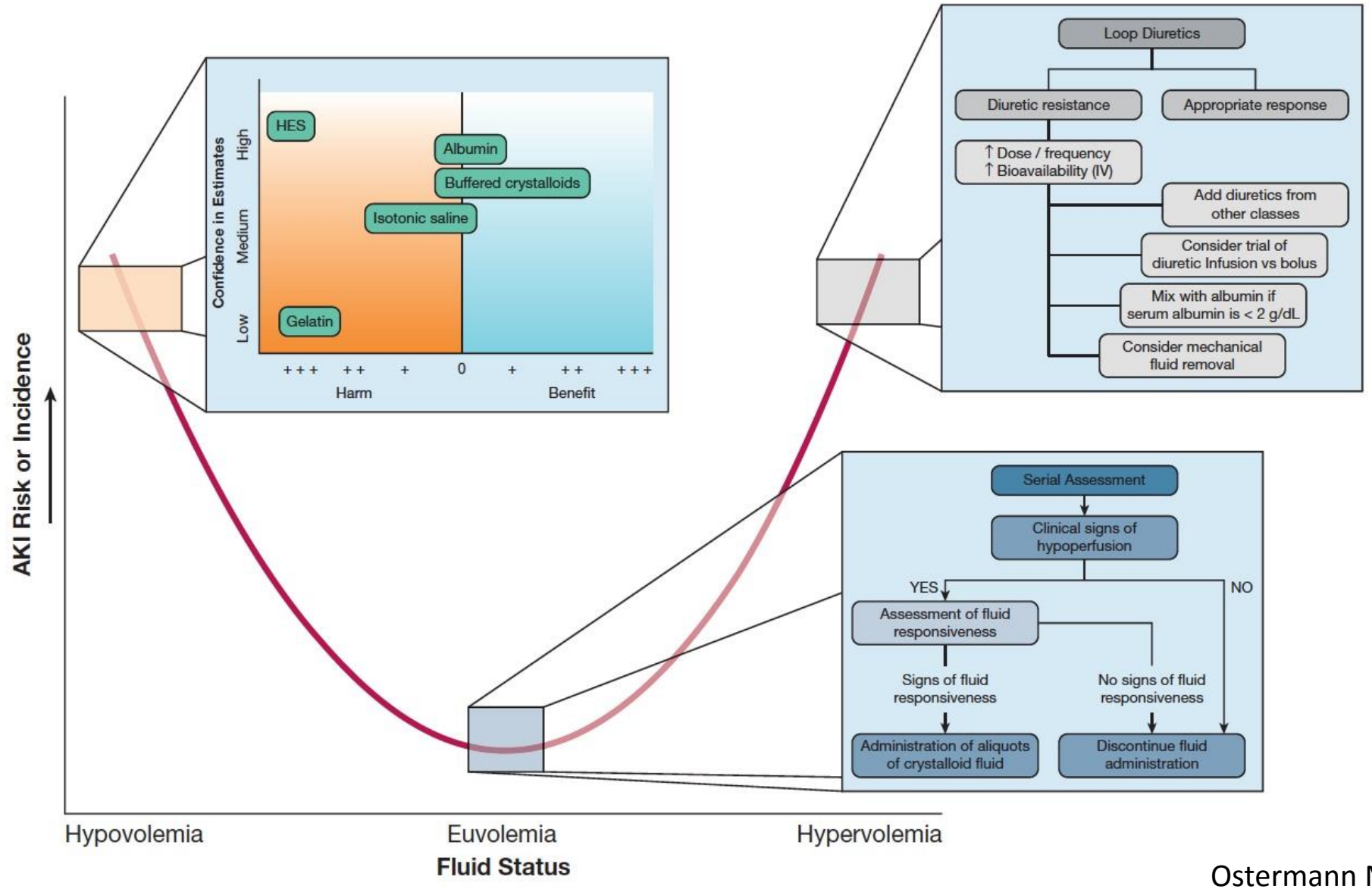
Phases of fluid resuscitation (The ROSE model)

	Rescue	Optimization	Stabilization	De-escalation
Goals	Life-saving	Organ rescue	Organ Support	Organ Recovery
Phenotype	Severe Shock	Unstable	Stable	Recovering
Fluid Therapy	Fluid Boluses	Fluid challenges	Neutral balance	Fluid removal

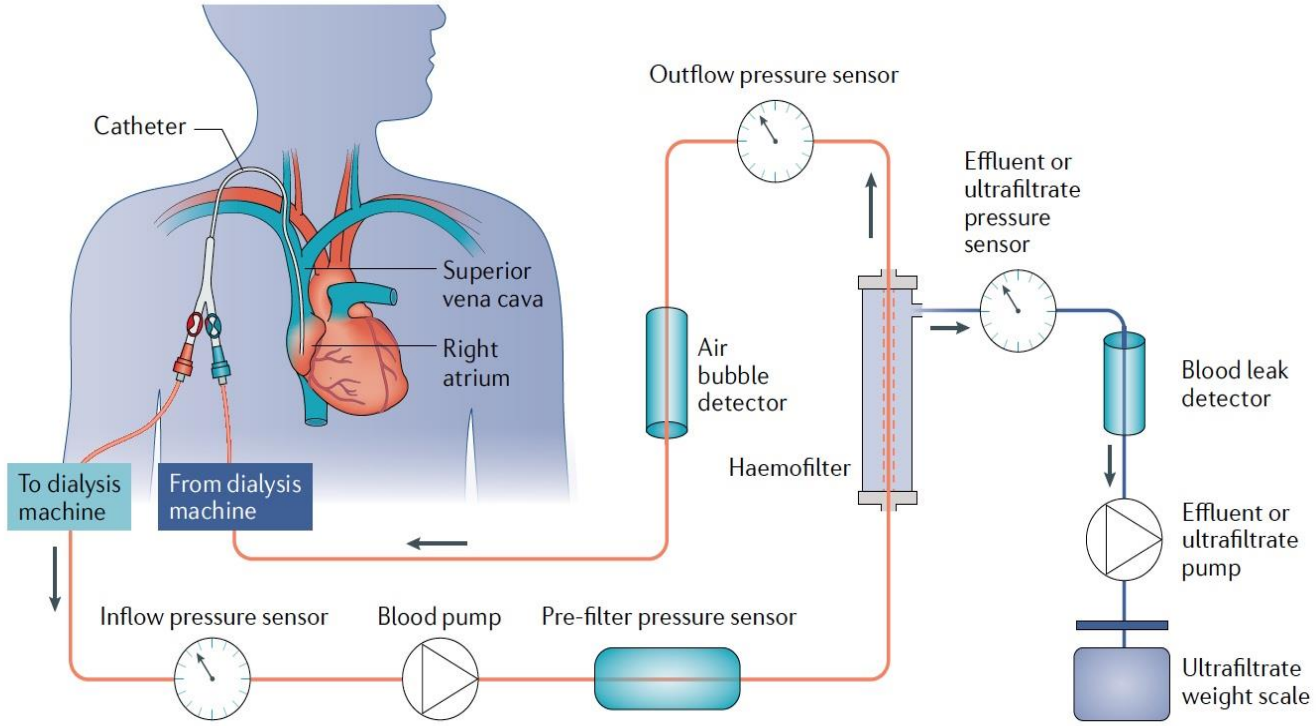


Hoste E.A., et al. British Journal Anaesthesia 2014

Fluid administration and the development of AKI



Ostermann M., et al. Chest 2019

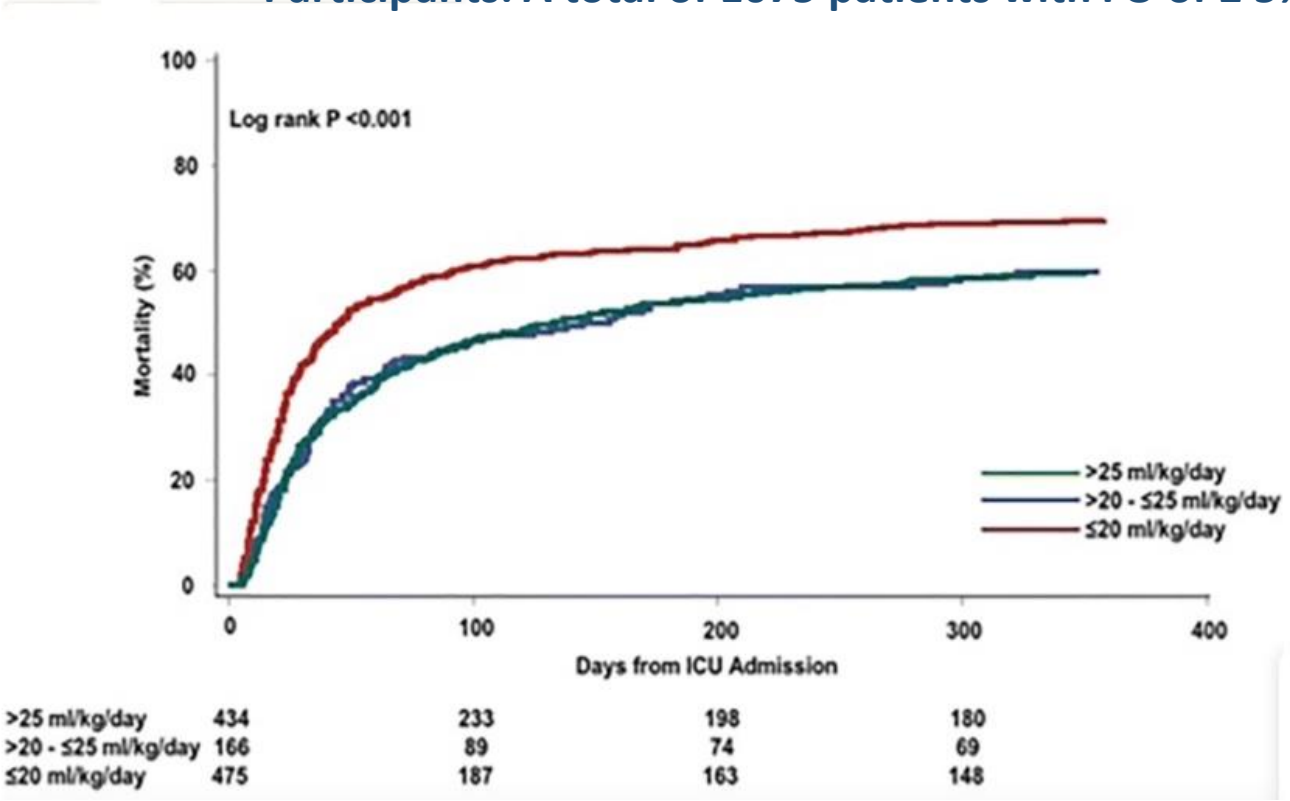


More than two third of patients with AKI are fluid overload at the initiation of KRT, despite fluid removal mortality remains >40% in these population.

Murugan R., et al. Nature reviews/nephrology 2020

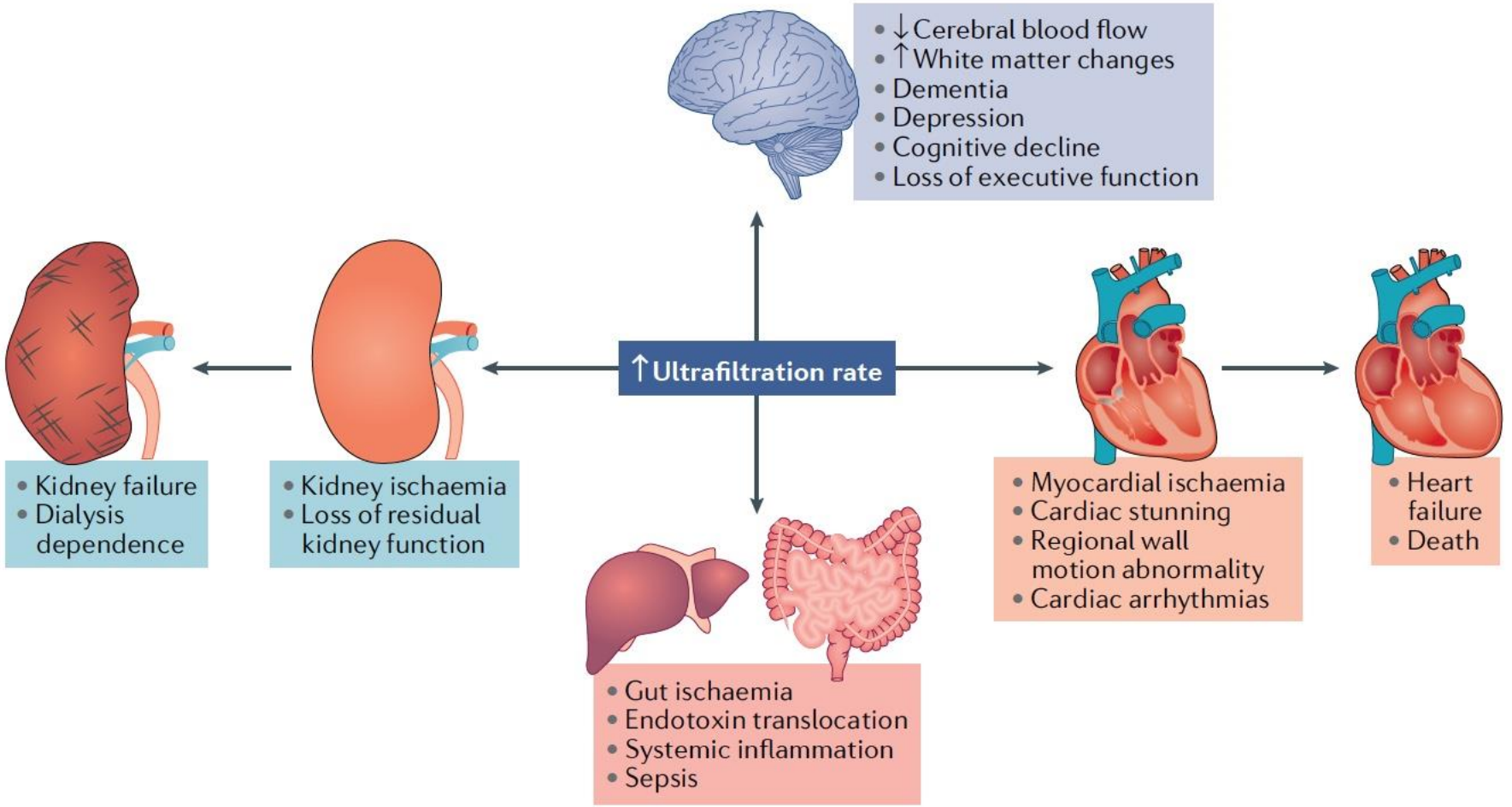
Higher net ultrafiltration intensity over a 24-hour is associated with lower 1-year mortality.

Participants: A total of 1075 patients with FO of ≥ 5%



Covariates	Unadjusted odds ratio (95% CI)	*p* value	Adjusted[a] odds ratio (95% CI)	*p* value
Moderate vs low-intensity UF^{NET} (reference)	0.65 (0.42–0.94)	0.024	0.81 (0.48–1.35)	0.41
High vs low-intensity UF^{NET} (reference)	0.64 (0.49–0.85)	0.002	0.61 (0.41–0.93)	0.02

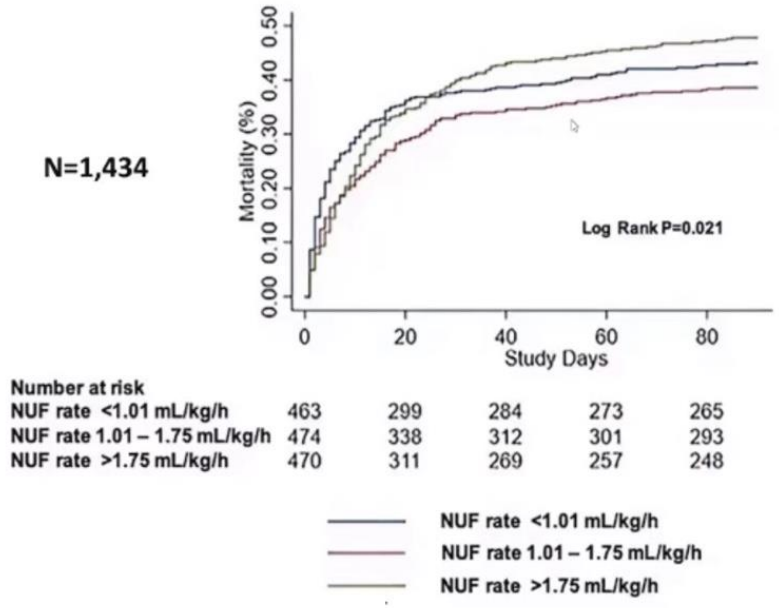
Murugan R., et al. critical Care 2018

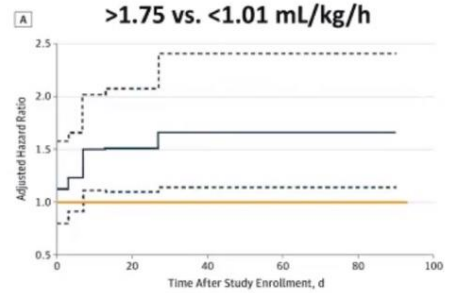


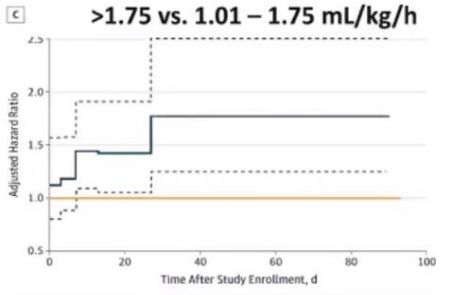
Murugan R., et al. Nature reviews/nephrology 2020

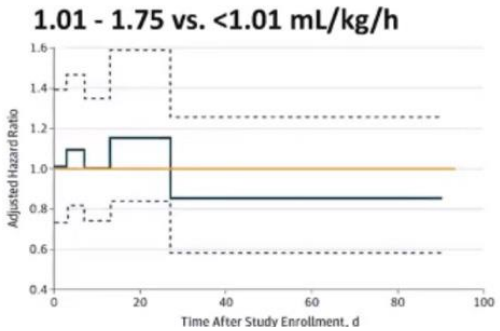
Net ultrafiltration and mortality, a secondary analysis of the results of the RENAL trial

Participants: A total of 1434 patients, not restricted patients to pre-defned level of FO









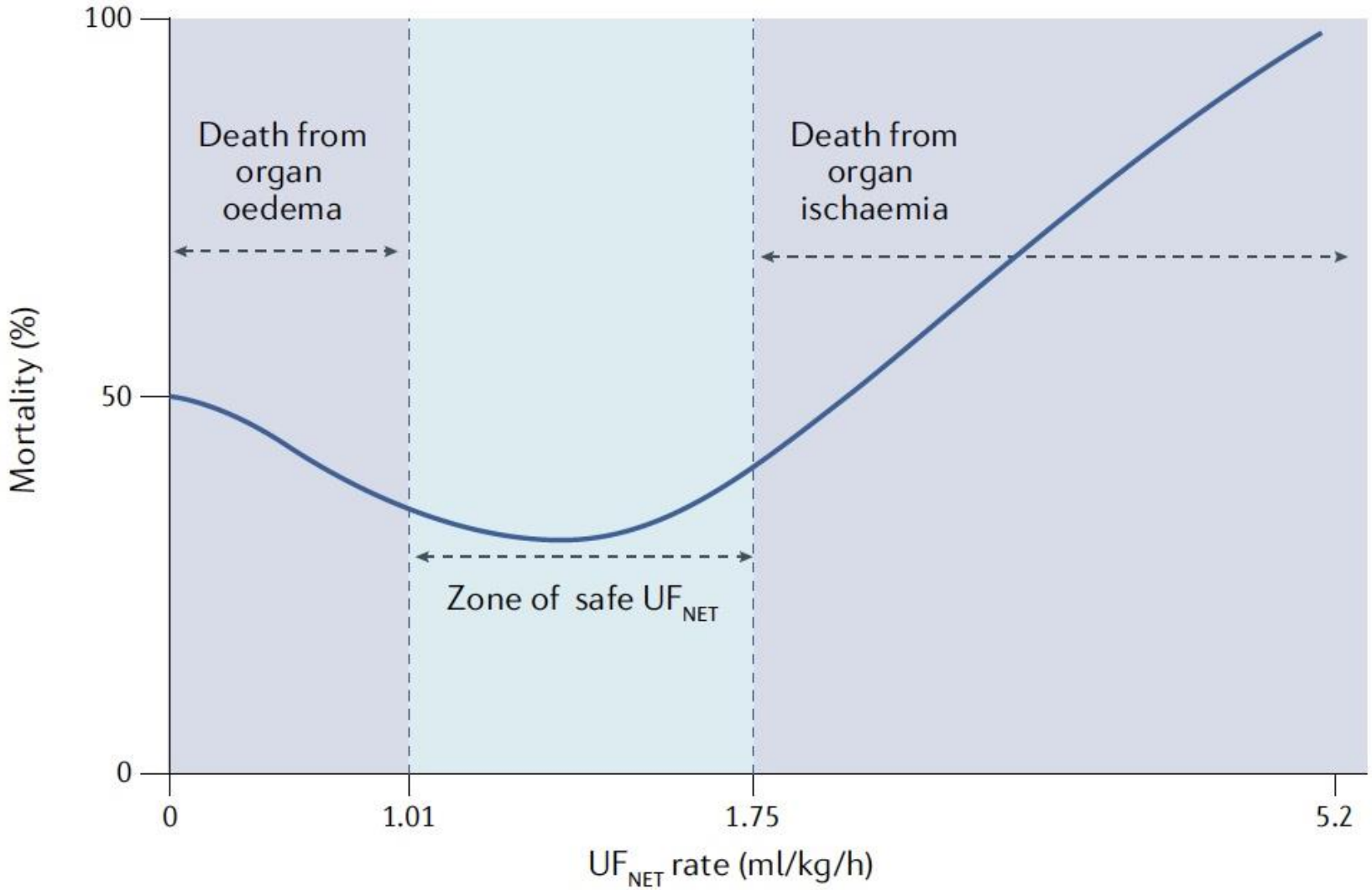
Net UF rates of >1.75 mL/kg/h, compared with <1.01 and 1.01-1.75 mL/kg/h, are associated with lower survival and renal recovery in patients treated with KRT

Murugan R.,et al. JAMA 2019

Table 1. Featured observational studies evaluating the association of UF_{NET} with clinical outcomes

Study	Sample	Independent Variable	Outcomes	Results	Comments
Murugan *et al.*, 2018 (14)	1075 adult patients with FO ≥5% before KRT initiation	UF_{NET}	1-year mortality	UF_{NET} intensity >25 versus ≤20 ml/kg per day was associated with lower 1-year risk-adjusted mortality	UF_{NET} was calculated as the net volume of fluid ultrafiltered per day from initiation of KRT until the end of ICU stay, adjusted for patient hospital admission body weight
Murugan *et al.*, 2019 (15)	1434 adult patients from RENAL trial	UF_{NET}	90-day mortality	UF_{NET} rates >1.75 ml/kg per (highest tertile) versus <1.01 ml/kg per hour (lowest tertile) were associated with lower survival	UF_{NET} was defined as the volume of fluid removed per hour, adjusted for patient body weight
Naorungroj *et al.*, 2020 (17)	347 adult patients	Early UF_{NET} (first 48 h of KRT)	28-day mortality	Early UF_{NET} rates >1.75 versus <1.01ml/kg per hour were associated with increased mortality	Early UF_{NET} was defined as the volume of fluid removed per hour, adjusted for patient body weight in the first 48 h
Naorungroj *et al.*, 2020 (18)	347 adult patients	UF_{NET}	Hospital mortality	UF_{NET} >1.75 ml/kg per hour was independently associated with increased hospital mortality, and this effect was not mediated by fluid balance, low BP, vasopressor use, hypokalemia, or hypophosphatemia	Interaction evaluation of UF_{NET} with possible mediators (fluid balance, hemodynamic status, key electrolytes) through mediation analysis
Serpa Neto *et al.*, 2020 (19)	1434 adult patients from RENAL trial	UF_{NET} evaluated in clusters of patients according to baseline characteristics	90-day mortality	Both high and low UF_{NET} rates may be harmful, especially in those with edema, sepsis, and greater acuity of illness	Two clusters of patients were identified; cardiovascular SOFA scores modulate the association of UF_{NET} with mortality
Murugan *et al.*, 2021 (20)	1433 adult patients from RENAL trial	UF_{NET}	Kidney recovery (alive and independent of KRT)	UF_{NET} rates >1.75 ml/kg per hour compared with rates 1.01–1.75 and <1.01 ml/kg per hour were associated with a longer duration of dependence on KRT	Competing risk multivariable regression models were used

UF_{NET}, net ultrafiltration rate; FO, fluid overload; KRT, kidney replacement therapy; ICU, intensive care unit; RENAL, Randomized Evaluation of Normal vs Augmented Level of Replacement Therapy; SOFA, Sequential Organ Failure Assessment.



Murugan R., et al. Nature reviews/nephrology 2020

The development of accurate methods for monitoring of intravascular volume during mechanical ultrafiltration is a key goal in hemodynamic management of patients on CRRT

Methods	Pitfalls
Conventionally used clinical parameters (i.e. blood pressure, CVP, peripheral edema,…)	Low sensitivity
Dynamic parameters, such as respiratory pulse pressure (PPV)and stroke volume variations (SVV) , inferior vena cava collapsibility and passive leg raising	Are not validated for fluid removal during CRRT
Hematocrit monitoring	Is not validated in critically ill patients
Point of care sonography (lung sonography, venous Doppler flow patterns of peripheral organs, …)	Is not validated for fluid removal during CRRT
BIVA (Bio-impedance vector analysis)	Is not validated for fluid removal during CRRT

Murugan R., et al. Nature reviews/nephrology 2020

Contents lists available at ScienceDirect

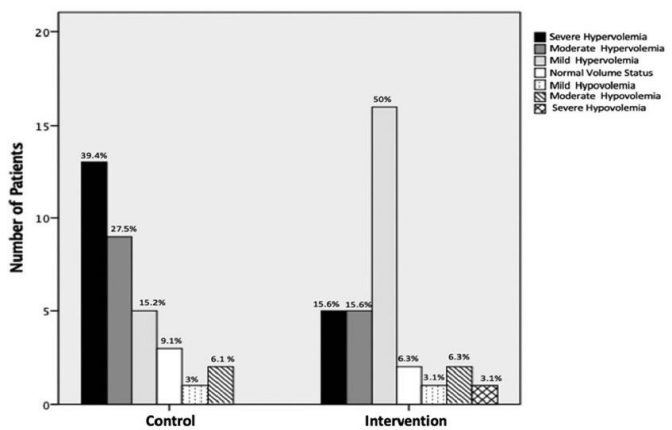
Journal of Critical Care

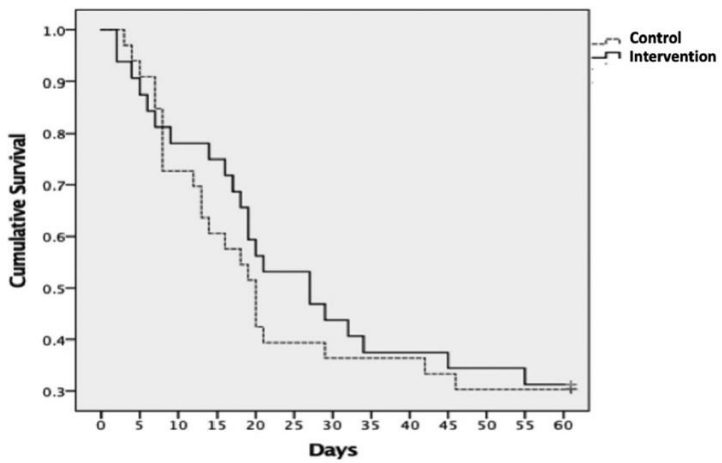
journal homepage: www.journals.elsevier.com/journal-of-critical-care

Applying bio-impedance vector analysis (BIVA) to adjust ultrafiltration rate in critically ill patients on continuous renal replacement therapy: A randomized controlled trial

Farin Rashid Farokhi [a,b,c,*], Effat Kalateh [d], Shadi Shafaghi [e], Antoine Guillaume Schneider [f,g], Seyed Mehdi Mortazavi [h], Hamidreza Jamaati [i], Seyed Mohammad Reza Hashemian [h,i]

	Intervention group N = 32	Control group N = 33	Odd ratio/ mean difference (95%CI)*	*P* value
Primary outcome				
The water content of LBM-percent	80.7 (9.36)	85.9 (10.4)	5.2 (0.2 to 10.1)	0.040
Secondary outcomes				
The duration of hospital admission-days	21.4 (15.1)	26.5 (21.5)	5.1(−4.1 to 14.3)	0.27
The duration of staying in the ICU-days	15.3 (14.7)	16.8 (17.1)	−1.5 (−9.7 to 6.6)	0.70
The length of being under MV-days	13.9 (15.3)	14.8(16.2)	−0.9 (−7.9 to 9.8)	0.83
Urine output during CRRT-cc/kg/h	0.9 (0.9)	0.5 (0.6)	0.6 (0.4 to 1.1)	0.035
The mortality rates:				
10 days	7 (21.9%)	9 (27.3%)	0.7 (0.2–2.3)	0.61
30 days	17 (53.1%)	20 (60.6%)	0.7 (0.3–2)	0.54
60 days	22 (68.8%)	21(63.6%)	1.3 (0.4–3.5)	0.66



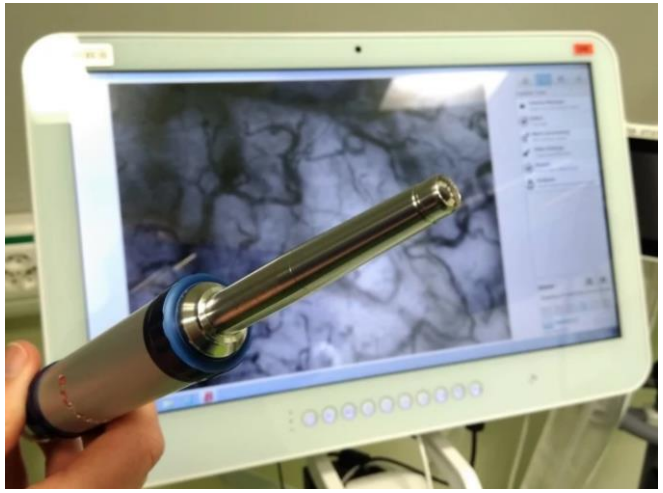


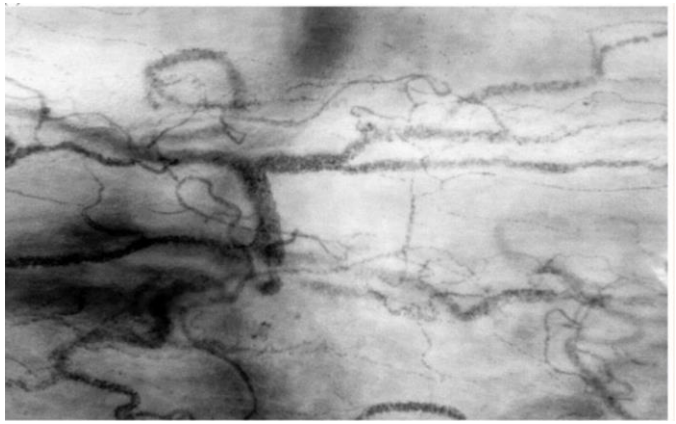
Rashid Farokhi F., et al. Journal of Critical Care 2022

Monitoring of sublingual microcirculation has potential to be used as a hemodynamic monitor to optimize the renal perfusion and oxygenation

- In critically ill patients, hemodynamic stabilization is not always associated with improvement in microcirculatory parameters.
- Dark-field microscopy, is a new bedside technique that allows direct observation of sublingual microcirculatory perfusion in real time.

- Functional capillary density (FCD) : length of all vessels containing RBCs per field of view
- Red blood cell velocity (RBCv): absolute blood flow velocity
- Capillary hematocrit (cHCT): hematocrit of blood in the capillary in a moment in time

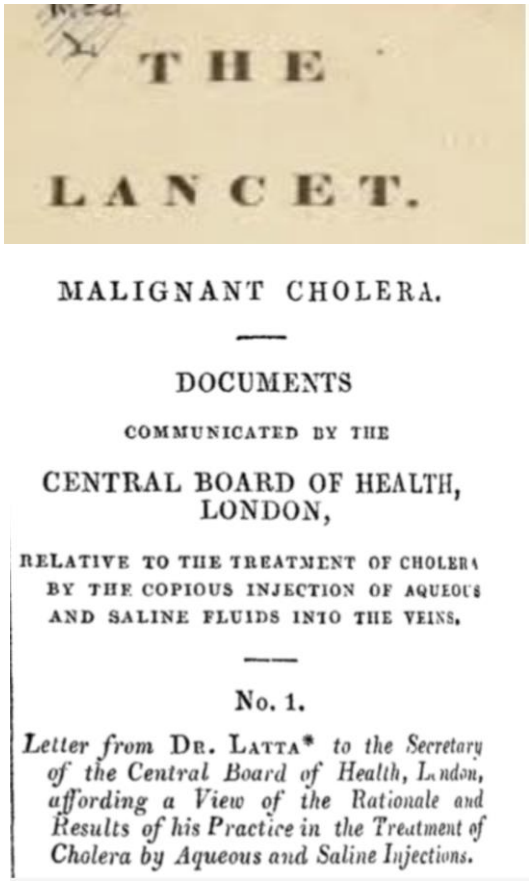




Ince C., et al. Intensive Care Med 2018

Summary

- There is growing evidence that in patients with or at risk of AKI, excessive fluid therapy beyond correction of hypovolemia may lead to AKI or worsening of kidney function.
- Oliguria per se is not an indication of fluid administration.
- The evaluation of both fluid tolerance and fluid responsiveness is suggested to be consider along with clinical examination in the decision to administer fluids in critically ill patients.
- Because of an increased risk of AKI, Hydroxyethyl starch is not recommended as fluid therapy in critically ill patients.
- In patients on KRT net UF rates have bidirectional relationship with mortality. Net UF rates of >1.75 mL/kg/h, compared with rates of 1-1.75 or<1 ml/kg/h, are associated with lower rates of patient survival and renal recovery.



THE

LANCET.

MALIGNANT CHOLERA.

DOCUMENTS

COMMUNICATED BY THE

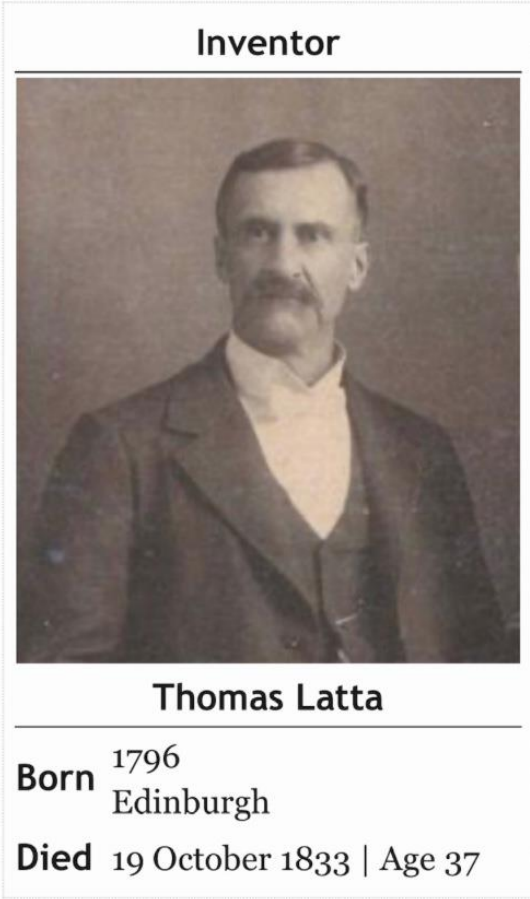
CENTRAL BOARD OF HEALTH, LONDON,

RELATIVE TO THE TREATMENT OF CHOLERA BY THE COPIOUS INJECTION OF AQUEOUS AND SALINE FLUIDS INTO THE VEINS.

No. 1.

Letter from Dr. Latta* *to the Secretary of the Central Board of Health, London, affording a View of the Rationale and Results of his Practice in the Treatment of Cholera by Aqueous and Saline Injections.*

Published in 1833



Despite a long history of using intravenous solutions, the clear answers to the fundamental questions regarding the optimal content, timing, rate, and the amount of fluid therapy remain unknown.