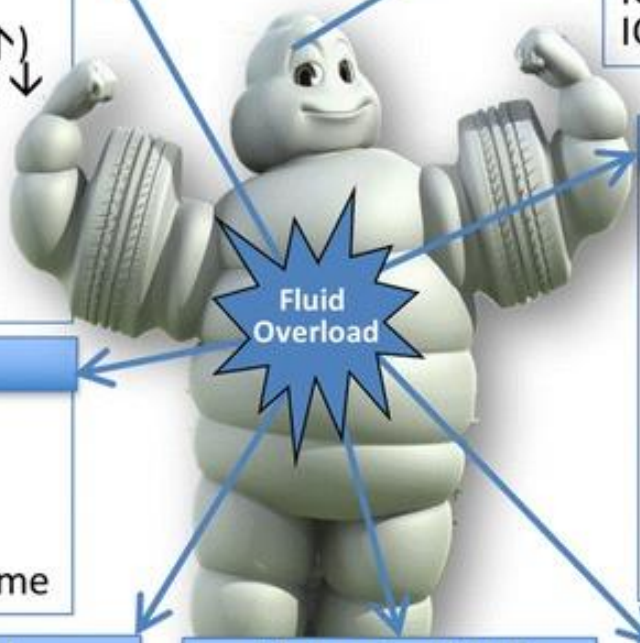
Fluid overload og Goal DIrected Fluid removal (GODIF)

Et kommende randomiseret multicenter studie

Sine Wichmann, afdelingslæge Nordsjællandshospital.

Fluid overload

- Iatrogent (væske resuscitation, medicinvand)
- Sygdomsbetinget (nyresvigt, sepsis, ect.)
- Organpåvirkning
- Estimering af hydreringstilstanden



Respiratory

Pulmonary edema ↑
Pleural effusion ↑
Altered pulmonary and chest wall elastance (cfr IAP ↑)
paO2 ↓ paCO2 ↑ PaO2/FiO2 ↓
Extra vascular lung water ↗
Lung volumes ↓ (cfr IAP ↑)
Prolonged ventilation ↑
Difficult weaning ↑
Work of breathing ↑

Central nervous system

Cerebral edema, impaired cognition, delirium
ICP ↑ CPP ↓ IOP ↑
ICH, ICS, OCS

Cardiovascular

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

Hepatic

Hepatic congestion ↑
Impaired synthetic function
Cholestatis ↑
Cytochrome P 450 activity ↓
Hepatic compartment syndrome

Gastrointestinal/visceral

Ascites formation ↑ Gut edema ↑
Malabsorption ↑ Ileus ↑
Bowel contractility ↓
IAP ↑ and APP (=MAP-IAP) ↓
Success enteral feeding ↓
Intestinal permeability ↑
Bacterial translocation ↑
Splanchnic microcirculatory flow ↓
ICG-PDR ↓, pHi ↓

Abdominal Wall

Tissue edema ↑
Poor wound healing ↑
Wound infection ↑
Pressure ulcers ↑
Abdominal compliance ↓

Renal

Renal interstitial edema
Renal venous pressure ↑
Renal blood flow ↓
Interstitial pressure ↑
Salt + water retention ↑
Uremia ↑ GFR ↓ RVR ↑
Renal CS

Malbrain et al. 2018

The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients

Garzotto et al. Critical Care 20 (2016).

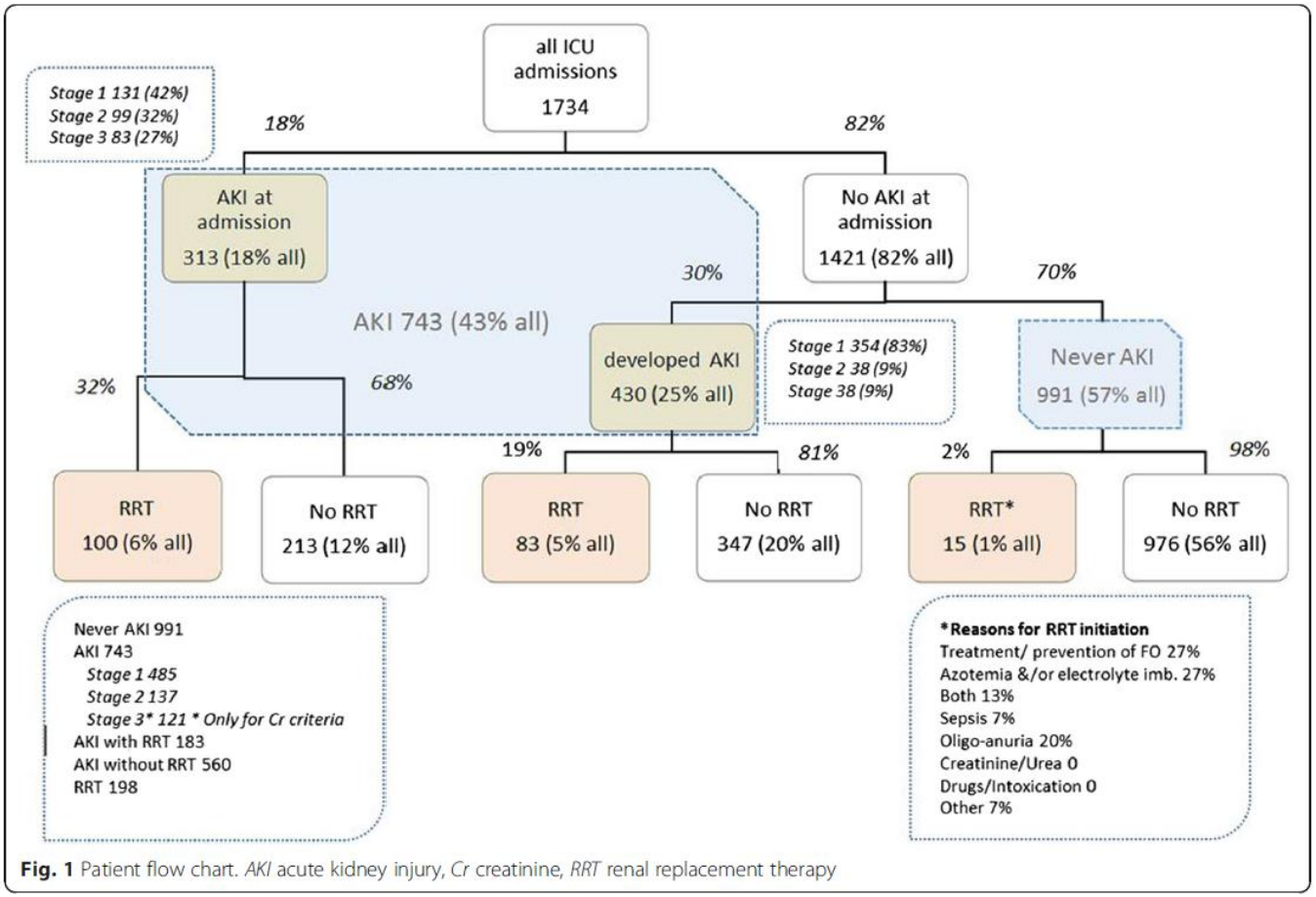


Fig. 1 Patient flow chart. *AKI* acute kidney injury, *Cr* creatinine, *RRT* renal replacement therapy

The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients

Garzotto et al. Critical Care 20 (2016)

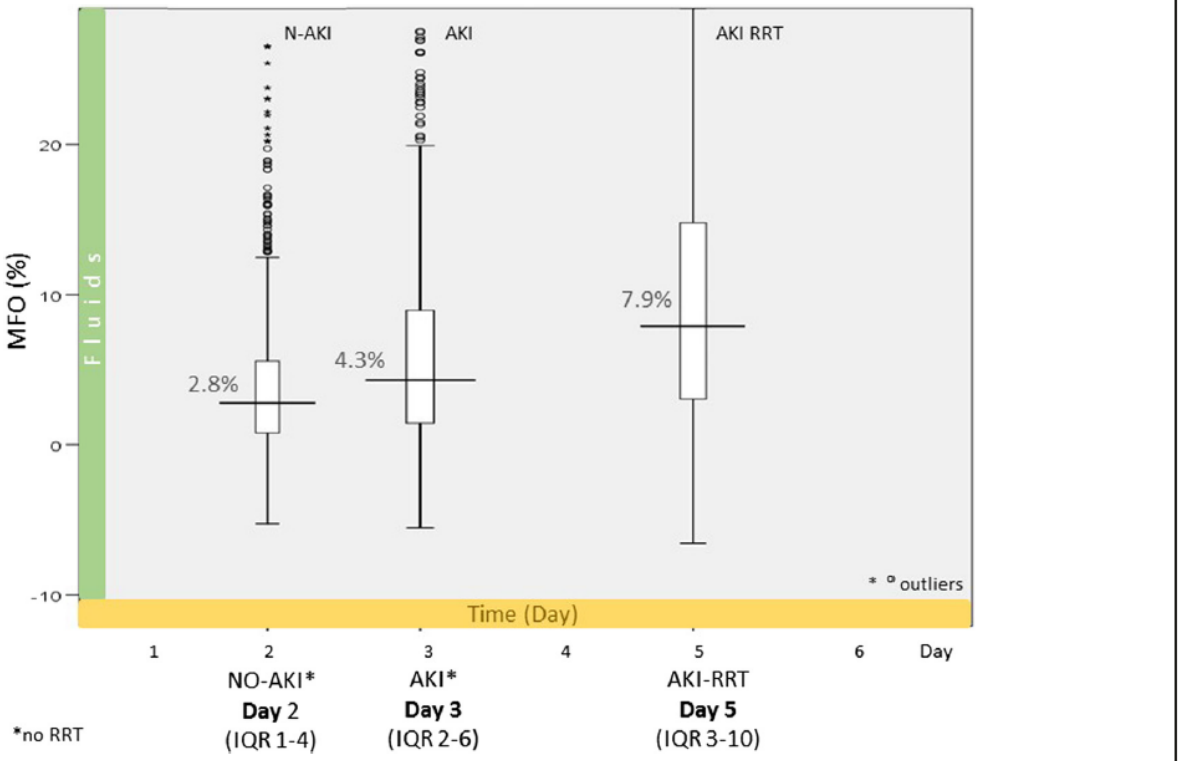


Fig. 4 Maximum FO (MFO) during ICU stay in N-AKI, AKI and AKI-RRT patients. MFO was higher in patients with AKI and particularly high in those treated with RRT. The horizontal axis shows the median day when MFO occurred. *AKI* patients with acute kidney injury, *AKI-RRT* patients with acute kidney injury treated with renal replacement therapy, *N-AKI* patients without AKI

The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients

Garzotto et al. Critical Care 20 (2016)

- ICU mortality: 22,3% hos patienter med AKI og 5,6% uden AKI.
- Hver 1% stigning i max fluid overload (MFO) er associeret til en OR på 1,075 for hospitals mortalitet (30 dage). Dette justeret for AKI, så var OR 1,044.
- Non-survivors kumulerede mere væske end survivors. Studiet viste også at væskeoverskud hos AKI patienterne var mere skadeligt ifht patienter med normal nyrefunktion.

Cumulative Fluid Balance and Mortality in Septic Patients with or without Acute Kidney Injury and Chronic Kidney Disease. Neyra JA et al. Crit Care Med 44, 1891–1900 (2016)

- Retrospektivt kohorte studie. 2632 patienter indlagt med svær sepsis, septisk shock og S-creatinin indenfor 3 mdr. før intensiv indlæggelsen. Ekskl: eGFR<15 ml/min/1,73m2 eller kronisk dialyse.
- Kumuleret VB efter 72 timer på intensiv afdelingen.
- 2632 patienter, 1211 med CKD, AKI forekom hos 1525 (57,9%) hvoraf 679 (44,5%) havde CKD.
- Hospitals mortalitet 603 (22,9%).
- Hver 1 liter stigning i kumuleret VB ved 72 timer var uafhængigt associeret til hospitalsmortalitet hos alle *uanset nyrefunktion*. Justeret OR: 1,06 (95% CI (1,04-1,08).
- AKI var ligeledes en uafhængig risiko faktor for død - justeret OR: 1,28.

Cumulative Fluid Balance and Mortality in Septic Patients with or without Acute Kidney Injury and Chronic Kidney Disease. Neyra JA et al. Crit Care Med 44, 1891–1900 (2016)

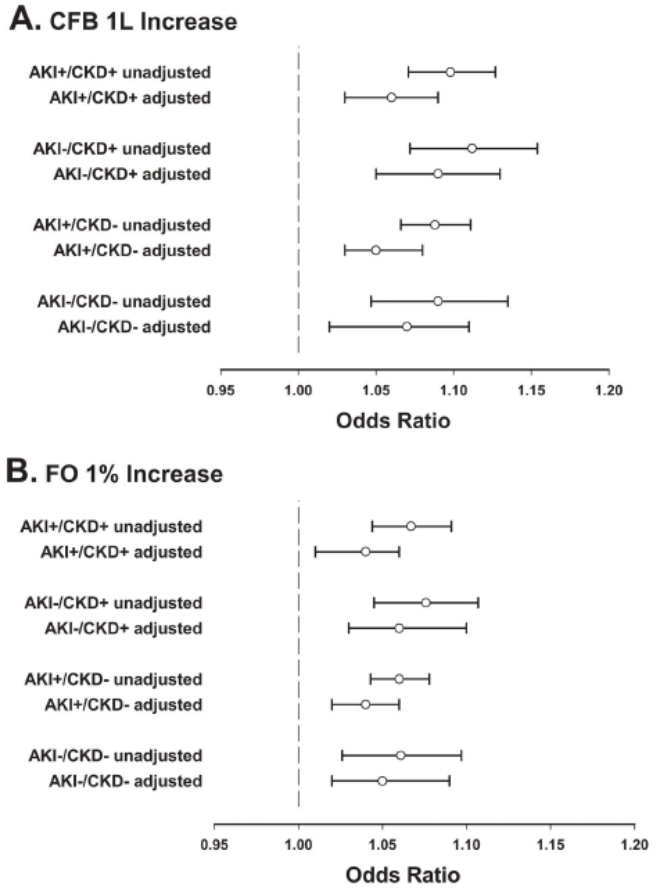


Figure 2.
Forest plots of unadjusted and adjusted odds ratios for hospital mortality in the primary cohort (n =2632). A) CFB per 1 L increase at 72 h of ICU admission. Adjusted odds ratio (95% CI) for hospital mortality in the entire cohort 1.06 (1.04 – 1.08); B) FO per 1% increase at 72 h of ICU admission. Adjusted odds ratio (95% CI) for hospital mortality in the entire cohort 1.04 (1.03 – 1.06). AKI =occurrence of acute kidney injury; CFB =cumulative fluid balance; CKD =pre-existing chronic kidney disease; FO =fluid overload percentage

Fluid accumulation during acute kidney injury in the intensive care unit.

R. E. Berthelsen et al. Acta Anaesthesiol.Scand 62, 936-944 (2018)

- Retrospektiv studie af alle indlagte AKI patienter på to danske intensiv afdelinger gennem 1 år.
- 863 inkluderede patienter. 460 (53%) udviklede 5% overhydrering og 254 (29%) udviklede 10% overhydrering. Der blev set på de første 5 døgns væskebalance.
- 28 dages mortalitet og renal recovery var nedsat allerede ved 5% overhydrering. 60% havde renal recovery. 33% døde – 25% af dem havde renal recovery inden de døde.

Fluid accumulation during acute kidney injury in the intensive care unit.

R. E. Berthelsen et al. Acta Anaesthesiol.Scand 62, 936-944 (2018)

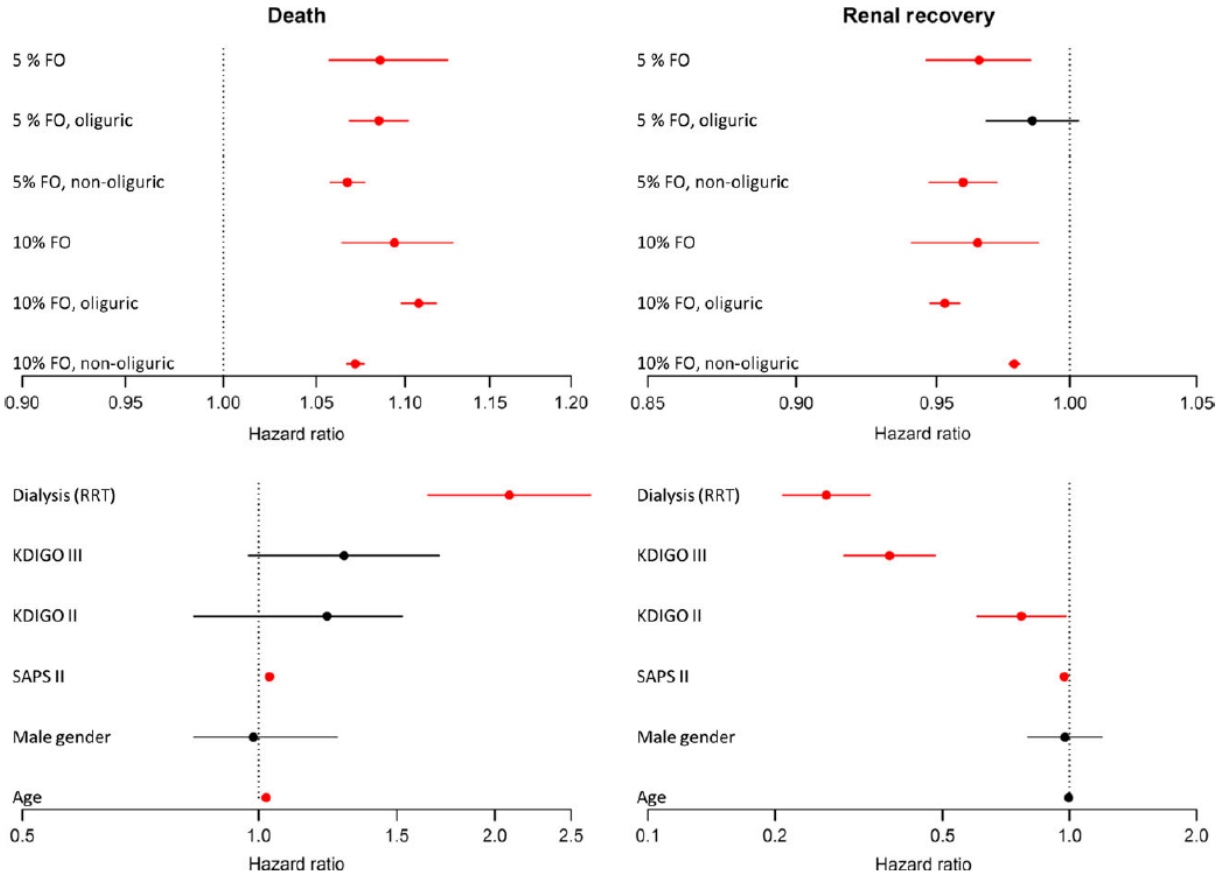


Fig. 3. Forest plot of joint model results. FO, Fluid overload; KDIGO, Kidney Disease Improving Global Outcome; SAPS II, Simplified Acute Physiology Score. [Colour figure can be viewed at wileyonlinelibrary.com]

SYSTEMATIC REVIEW

Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis

Jonathan A. Silversides[1,2*], Emmet Major[2], Andrew J. Ferguson[3], Emma E. Mann[2], Daniel F. McAuley[1,4], John C. Marshall[5,6], Bronagh Blackwood[1] and Eddy Fan[5]

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Abstract

Background: It is unknown whether a conservative approach to fluid administration or deresuscitation (active removal of fluid using diuretics or renal replacement therapy) is beneficial following haemodynamic stabilisation of critically ill patients.

Purpose: To evaluate the efficacy and safety of conservative or deresuscitative fluid strategies in adults and children with acute respiratory distress syndrome (ARDS), sepsis or systemic inflammatory response syndrome (SIRS) in the post-resuscitation phase of critical illness.

Methods: We searched Medline, EMBASE and the Cochrane central register of controlled trials from 1980 to June 2016, and manually reviewed relevant conference proceedings from 2009 to the present. Two reviewers independently assessed search results for inclusion and undertook data extraction and quality appraisal. We included randomised trials comparing fluid regimens with differing fluid balances between groups, and observational studies investigating the relationship between fluid balance and clinical outcomes.

Results: Forty-nine studies met the inclusion criteria. Marked clinical heterogeneity was evident. In a meta-analysis of 11 randomised trials (2051 patients) using a random-effects model, we found no significant difference in mortality with conservative or deresuscitative strategies compared with a liberal strategy or usual care [pooled risk ratio (RR) 0.92, 95 % confidence interval (CI) 0.82–1.02, $I^2 = 0$ %]. A conservative or deresuscitative strategy resulted in increased ventilator-free days (mean difference 1.82 days, 95 % CI 0.53–3.10, $I^2 = 9$ %) and reduced length of ICU stay (mean difference −1.88 days, 95 % CI −0.12 to −3.64, $I^2 = 75$ %) compared with a liberal strategy or standard care.

Conclusions: In adults and children with ARDS, sepsis or SIRS, a conservative or deresuscitative fluid strategy results in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care. The effect on mortality remains uncertain. Large randomised trials are needed to determine optimal fluid strategies in critical illness.

Er overhydrering en sygdomsmarkør eller en iatrogen risikofaktor?

Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Hjortrup et al. Intensiv Care Med. 42, 1695-1705 (2016)

Table 2 Primary and secondary outcome measures

Outcome	Fluid restriction group ($n = 75$)	Standard care group ($n = 76$)	Fluid restriction vs. standard care (95 % CI)[a]	*P* value
Co-primary outcome measures				
Volumes of resuscitation fluid (mL)				
First 5 days after randomisation	500 (0 to 2500) [1687]	2000 (1000 to 4100) [2928]	−1241 (−2043 to −439)	<0.001[b]
During ICU stay after randomisation	500 (0 to 3250) [1992]	2200 (1000 to 4750) [3399]	−1407 (−2358 to −456)	<0.001[b]
Secondary outcome measures				
Total fluid input (mL)[c]				
First 5 days after randomisation	12,411 (5518 to 17,035) [11,777]	13,687 (7163 to 17,082) [12,597]	−820 (−2968 to 1329)	0.45
During ICU stay after randomisation	18,291 (5518 to 34,045) [21,459]	16,970 (7163 to 29,889) [23,495]	−2036 (−10,920 to 6848)	0.65
Cumulated fluid balance (mL)				
First 5 days after randomisation	1752 (−1153 to 3758) [2141]	2680 (407 to 5114) [3289]	−1148 (−2531 to 235)	0.06[b]
During ICU stay after randomisation	1923 (−1964 to 5415) [2,032]	2014 (−168 to 4678) [2507]	−475 (−2254 to 1304)	0.60
Serious adverse reactions[d]				
Number of reactions per day during the ICU stay	0.14 (0 to 0.50) [0.37][e]	0.15 (0 to 0.52) [0.33][e]	NA	0.85[b]

Values in the two intervention groups are presented as medians (interquartile ranges) [estimated mean values adjusted for trial site] unless otherwise specified

A total of 33 patients (8 had died and 25 had been discharged) and 32 (7 had died and 25 had been discharged) were not in the ICU on day 5 in the fluid restriction group and the standard care group, respectively. The ICU length of stay was median 6 days (IQR 3–11) and 5 (3–10) in the fluid restriction group and the standard care group, respectively

CI confidence interval, *NA* not applicable

[a] Estimated mean of the restrictive group minus estimated mean of the standard care group

[b] Non-parametric *p* values. The estimated differences are presented where applicable even though the assumptions for parametric testing were not fully met

[c] The total input of non-resuscitation fluids is presented in Table S16 in ESM 1

[d] Serious adverse reactions to isotonic crystalloids and norepinephrine were recorded daily as anaphylaxis, hypernatraemia, hyperchloraemic acidosis, seizures, central pontine myelinolysis, cerebral haemorrhage, cardiac arrhythmia or delirium

[e] Observed mean presented

De-resuscitation

- Hvornår?
- Hvordan?
- Hvor hurtigt?

Forced fluid removal in intensive care patients with acute kidney injury: The randomised FFAKI feasibility trial. Berthelsen et al. Acta Anaesthesiol. Scand, 62, 936-944 (2018)

Inclusion criteria
Age ≥18 y of age
AND
Acute Kidney Injury defined according to the KDIGO criteria as either
- Increase in SCr by ≥26.5 µmol/L within 48 h; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 d
AND
Renal Recovery Score ≤ 60%.
AND
Fluid accumulation of more than 10% of ideal body weight.
AND
Able to undergo randomization within 12 h of fulfilling the other inclusion criteria
Exclusion criteria
Known allergy to furosemide or sulphonamides
OR
Known pre-hospitalization advanced chronic kidney disease
- (eGFR < 30 mL/min/1.73 m^2 or chronic RRT).
OR
Severe hypoxic respiratory failure (use of invasive ventilation and FiO2 >80% and PEEP >10 cm H_2O)
OR
Severe burn injury (≥10% TBSA)
OR
Severe dysnatremia (<120 or >155 mmol/L)
OR
Hepatic coma
OR
Mentally disabled undergoing forced treatment
OR
Pregnancy/breast feeding
OR
Lack of commitment for on-going life support including RRT
OR
Lack of informed consent

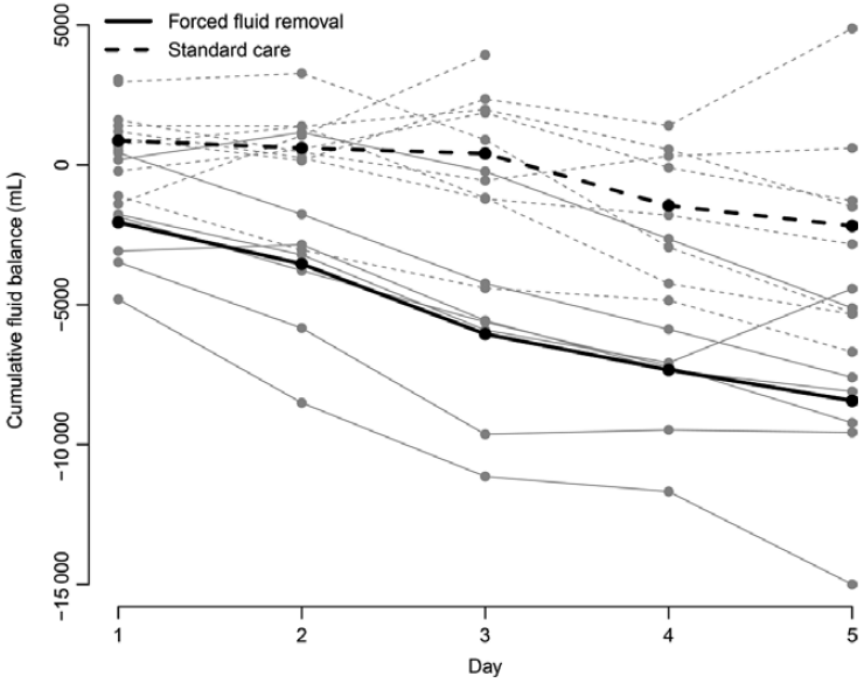


FIGURE 4 Cumulated daily fluid balance in all patients during day 1-5 after randomisation, separated according to allocation. Bold lines represent mean values

CRRT som redskab under deresusciationen

- Dette endnu ikke undersøgt hos patienter uden AKI.
- Flere studier har undersøgt tidlig versus sen opstart i dialyse hos AKI patienter med divergerende resultater.
- 3 større randomiserede studier: ELAINE (2016), AKIKI (2016) og IDEAL-ICU (2018).

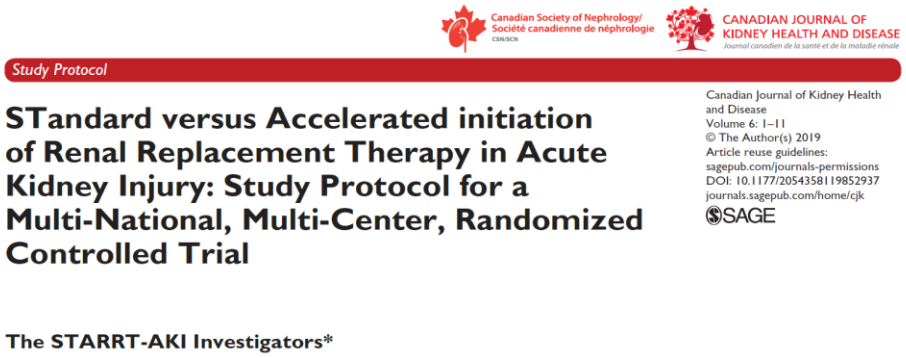
Table 2 Recent studies investigating different aspects of timing of renal replacement therapy in critically ill patients

Study	ELAIN [21••]	AKIKI [24••]	IDEAL-ICU [23••]	STARRT-AKI
Year	2016	2016	2018	Ongoing
Design	RCT	RCT	RCT	RCT
Setting	Single centre, Germany	Multicentre, France	Multicentre, France	Multicentre
Population	KDIGO 2 Blood NGAL > 150 ng/ml One of: • Sever sepsis • Fluid overload • Worsening SOFA • Receiving vasoactive support	KDIGO 3 Receiving mechanical ventilation or vasopressor therapy No absolute indication for RRT*	RIFLE F Early septic shock (< 48 h of vasoactive medication) No absolute indication for RRT[1]	Severe AKI[2]
N	231 (50% Post cardiac surgery)	620 (Mixed ICU)	488 (Mixed ICU) (stopped for futility. Target 864)	2866 (Target)
Early RRT strategy	< 8 h from KDIGO stage 2	< 6 h of KDIGO stage 3	< 12 h from RIFLE F	< 12 h from eligibility
Late RRT strategy	< 12 h from KDIGO stage 3 AKI or absolute indication*	Oliguria for > 72 h BUN > 15 mg/dL or absolute indication[1]	48 h from RIFLE F (unless recovered) or absolute indication[1]	Absolute indication[1] or persistent AKI > 72 h
Delivery of intervention early group	100% received RRT (100% CRRT)	98% received RRT (44% CRRT as first modality) (33% CRRT only)	97% received RRT	Awaiting data
Delivery of intervention late group	91% received RRT (100% CRRT)	51% received RRT (45% CRRT as first modality) (30% CRRT only)	62% received RRT (17% due to absolute indication[1])	Awaiting data
Primary outcome	90-day mortality	60-day mortality	90-day mortality	90-day mortality
Outcome (early vs. late)	39.3% vs. 53.6% ($p = 0.03$)	48.5% vs. 49.7% ($p = 0.79$)	58% vs. 54% ($p = 0.38$).	Awaiting data

RRT renal replacement therapy, *CRRT* continuous renal replacement therapy, *RCT* randomized controlled trial, *KDIGO* Kidney Disease Improving Global Outcomes, *AKI* acute kidney injury, *RIFLE* Risk, Injury, Failure, Loss and End-stage renal disease, *NGAL* neutrophil gelatinase–associated lipocalin, *BUN* blood urea nitrogen, *SOFA* Sequential Organ Failure Assessment

[1] Absolute indications include: Severe hyperkalemia, severe metabolic acidosis, hypoxemic respiratory failure due to fluid overload

[2] Defined as (1) twofold increase in serum creatinine, (2) serum creatinine ≥ 354 μmol/l and a minimum increase of 27 μmol/l, or (3) urine output < 6 ml/kg in 12 h



Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE

Study Protocol

STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury: Study Protocol for a Multi-National, Multi-Center, Randomized Controlled Trial

Canadian Journal of Kidney Health and Disease
Volume 6: 1–11
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The STARRT-AKI Investigators*

- RCT
- 170 centre over hele verden
- Vil inkludere 2866 intensiv patienter med AKI
- I marts 2019 var der inkluderet 2623 patienter
- 90 dages ”all cause mortality”
- Afventer resultaterne

Murugan et al. Critical Care (2018) 22:223
https://doi.org/10.1186/s13054-018-2163-1

Critical Care

RESEARCH Open Access

Net ultrafiltration intensity and mortality in critically ill patients with fluid overload

Raghavan Murugan[1,2,7*], Vikram Balakumar[1,2], Samantha J. Kerti[2], Priyanka Priyanka[1,2], Chung-Chou H. Chang[1,2,3,4], Gilles Clermont[2], Rinaldo Bellomo[5], Paul M. Palevsky[1,3,6] and John A. Kellum[1,2]

Abstract

Background: Although net ultrafiltration (UF^{NET}) is frequently used for treatment of fluid overload in critically ill patients with acute kidney injury, the optimal intensity of UF^{NET} is unclear. Among critically ill patients with fluid overload receiving renal replacement therapy (RRT), we examined the association between UF^{NET} intensity and risk-adjusted 1-year mortality.

Methods: We selected patients with fluid overload ≥ 5% of body weight prior to initiation of RRT from a large academic medical center ICU dataset. UF^{NET} intensity was calculated as the net volume of fluid ultrafiltered per day from initiation of either continuous or intermittent RRT until the end of ICU stay adjusted for patient hospital admission body weight. We stratified UF^{NET} as low (≤ 20 ml/kg/day), moderate (> 20 to ≤ 25 ml/kg/day) or high (> 25 ml/kg/day) intensity. We adjusted for age, sex, body mass index, race, surgery, baseline estimated glomerular filtration rate, oliguria, first RRT modality, pre-RRT fluid balance, duration of RRT, time to RRT initiation from ICU admission, APACHE III score, mechanical ventilation use, suspected sepsis, mean arterial pressure on day 1 of RRT, cumulative fluid balance during RRT and cumulative vasopressor dose during RRT. We fitted logistic regression for 1-year mortality, Gray's survival model and propensity matching to account for indication bias.

Results: Of 1075 patients, the distribution of high, moderate and low-intensity UF^{NET} groups was 40.4%, 15.2% and 44.2% and 1-year mortality was 59.4% vs 60.2% vs 69.7%, respectively ($p = 0.003$). Using logistic regression, high-intensity compared with low-intensity UF^{NET} was associated with lower mortality (adjusted odds ratio 0.61, 95% CI 0.41–0.93, $p = 0.02$). Using Gray's model, high UF^{NET} was associated with decreased mortality up to 39 days after ICU admission (adjusted hazard ratio range 0.50–0.73). After combining low and moderate-intensity UF^{NET} groups ($n = 258$) and propensity matching with the high-intensity group ($n = 258$), UF^{NET} intensity > 25 ml/kg/day compared with ≤ 25 ml/kg/day was associated with lower mortality (57% vs 67.8%, $p = 0.01$). Findings were robust to several sensitivity analyses.

Conclusions: Among critically ill patients with ≥ 5% fluid overload and receiving RRT, UF^{NET} intensity > 25 ml/kg/day compared with ≤ 20 ml/kg/day was associated with lower 1-year risk-adjusted mortality. Whether tolerating intensive UF^{NET} is just a marker for recovery or a mediator requires further research.

Keywords: Net ultrafiltration, Intensity, Fluid overload, Renal replacement therapy, Dialysis, Mortality

GOal DIrected Fluid removal (GODIF)
Et randomiseret multicenter studie

- Formål:
  - Undersøge om kontrolleret væsketræk/de-resuscitation hos intensiv patienter med væskeoverskud på ≥ 5% sænker mortaliteten.

Randomiseret multicenter studie

- Klinisk randomiseret studie på intensiv afdelinger.

- **Intervention**: goal directed fluid removal med formål at opnå neutral væskebalance så hurtigt som muligt og vedligeholde den efterfølgende.
- **Randomisering**: kontrolleret væsketræk vha. furix infusion/CRRT eller til standard behandling.

- Ca. 1000 patienter.

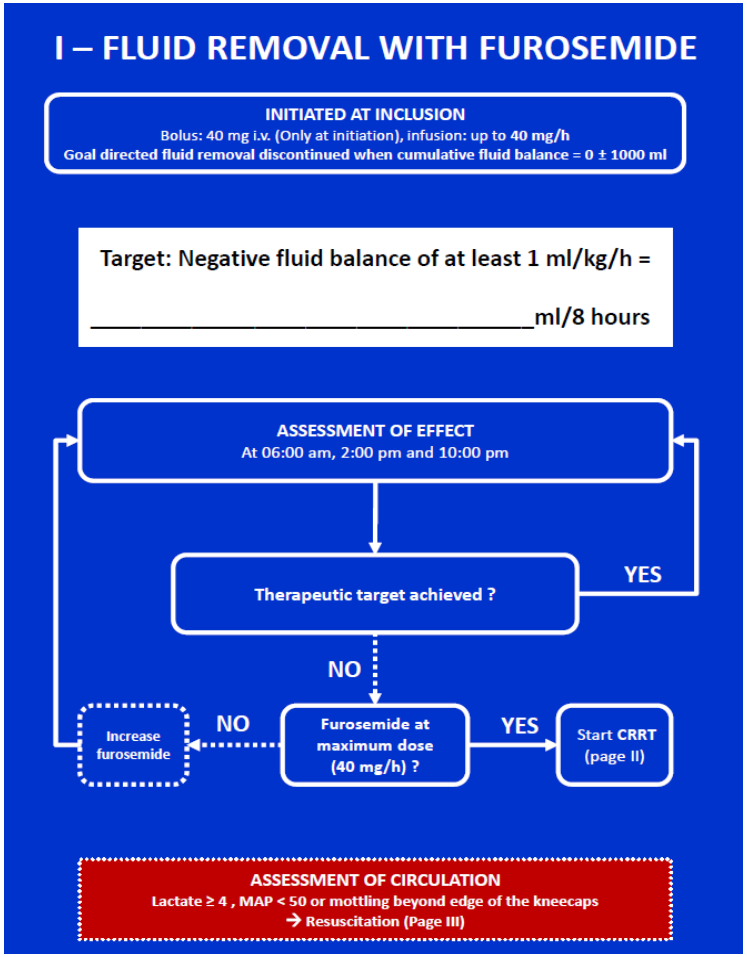
Inklusions kriterier:

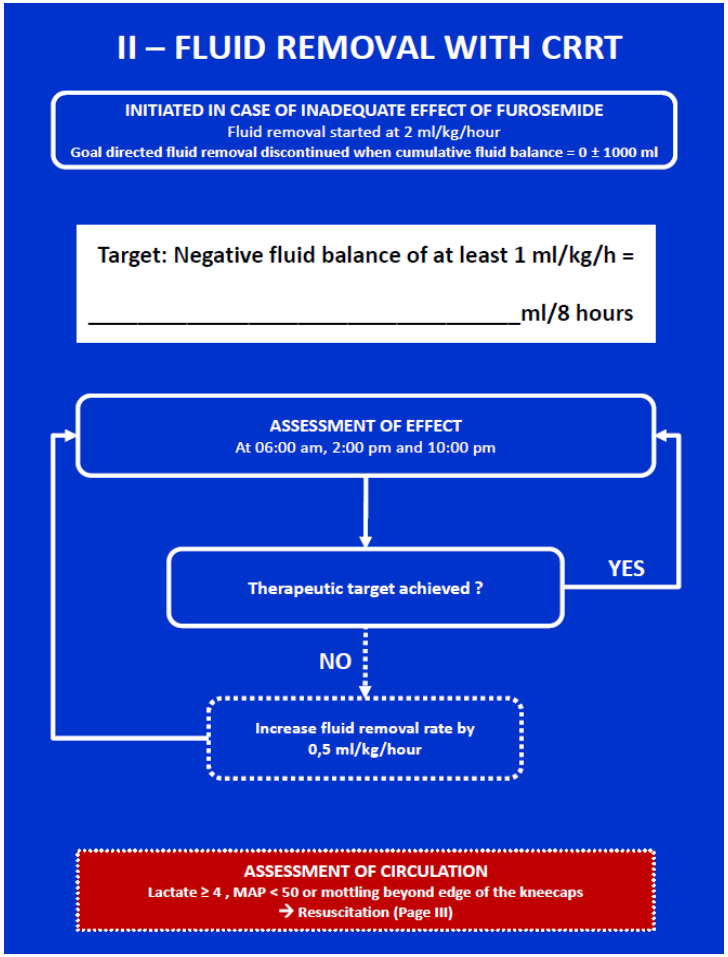
- Alder ≥ 18 år
- Overhydrering - defineret som positiv væskebalance på ≥ 5% udregnet ud fra IBW.

Ekslusions kriterier:

- Kronisk nyresvigt (eGFR < 30 ml/minut/1.73 m2 eller kronisk dialyse).
- Hypoksisk respiratorisk svigt (mekanisk ventilation, FiO_2 > 0.80 and PEEP > 10 cm H_20).
- Brandsår (TBSA ≥ 10%)
- Svært leversvigt
- Dysnatriæmi (< 120 eller > 155 mmol/l).
- Under tvang.
- Gravid eller ammende.
- Behandlingsbegrænsninger for dialysebehandling.
- Allergi overfor furosemid eller sulfonamider.
- Manglende informeret samtykke

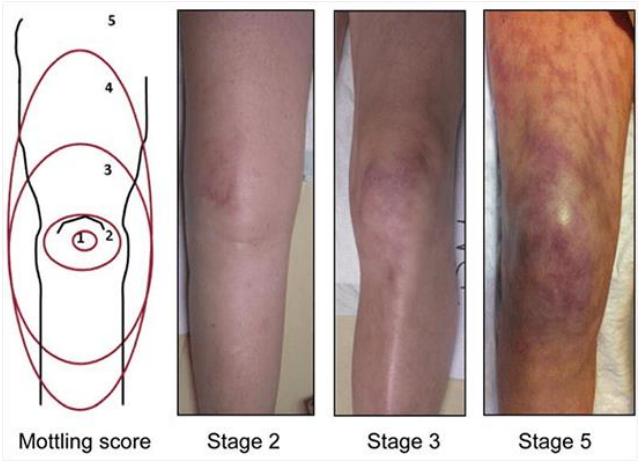
Intervention





Intervention – pause/resuscitation

- I tilfælde af én af følgende skal væsketrækket standses:
  - MAP < 50 mmHg - resistent for vasopressor
  - P-laktat ≥ 4 mmol/l
  - Marmorering ud over knæskallerne



Intervention – pause/resuscitation

- Giv 250-500 ml krystalloid
- Re-evaluer cirkulationen indenfor 30 min
- Gentag væske-resuscitation indtil tilfredsstillende cirkulation.
- Cirkulationen skal være stabil i minimum 1 time
- Genstart væsketræk med 25% reduceret dosis i minimum 4 timer før evaluering af effekt.

Kontrol gruppen

- Spontan afvanding.
- Vanlige loop diuretika kan doseres ved at omlægge til iv equivalenter. Andre diuretika må ikke bruges.
- Yderligere furosemid må kun anvendes ved:
  - Respiratorisk insuff. (P/F-ratio < 26 kPa (200 mmHg) og lungeødem som behandlende læge vurderer at skyldes overhydrering.

CRRT i kontrol gruppen må kun opstartes ved nedstående kriterier:

- Hyperkaliæmi (p-K > 6 mmol/l)
- Svær metabolisk acidose pga. AKI (pH < 7.20 og SBE < -10 mmol/l) resistent overfor iv bicarbonate infusion.
- Stort væskeoverskud kombineret med hypoksisk respiratorisk svigt (P/F-ratio < 26 kPa (200 mmHg)).
- Vedvarende AKI >72 timer (oliguri/anuri eller S-kreatinin ikke er faldet til <50% ifht. kreatinin ved inklusionen).
- Forgiftning
- Hypertermi

Primære outcome

- All cause mortalitet ved 90 dage

Sekundære outcomes

- All cause mortality efter 1 år
- Antal dage i live undenfor hospital ved 90 dage.
- Dage i live uden mekanisk ventilation, vasopressor og dialyse ved 90 dage.
- Antal patienter der udvikler AKI.
- Renal Recovery.
  - Defineret som 5 efterfølgende dage uden behov for dialyse og S-kreatinine < 150% ud fra udgangsværdien.
- Akkumulerede antal SAR/SAEér under intensiv indlæggelsen.
- HRQoL 1 år efter randomiseringen vha. EUroQoL (EQ)-5D-5L og EQ-VAS scorer
- Kognitiv funktion1 år efter randomiseringen vha. MoCa score.

Proces variable:

- Kumulativ VB 5 døgn efter randomisering (eller ved udskrivelse).
- Gennemsnitlig daglig VB under indlæggelsen på intensiv afdelingen.
- Kumulativ VB under hele intensiv indlæggelsen.
- Tid indtil normal væskebalance opnås.

Spørgsmål?

Tak for opmærksomheden!